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IF GIN VELD PLAFOD.

Francis Weld Peabody

Francis Weld Peabody was born at Cambridge, Massachusetts, November 24, 1881, and died at the same place October 13 1927. His ancestors were New England people of high character and distinguished ability. His father was formerly a professor at Harvard University and later Dean of the Harvard Divinity School. He received through inheritance a sound body and a good brain, and from his early environment, which was the best that this country offers, he undoubtedly acquired the "gentleness and unshaken adherence to judgments deliberately formed, indifference to outward show and compliment, industry and assiduity," that were to distinguish him throughout his life.

He graduated from Harvard College in 1903, and the same year he entered the Harvard Medical School where he showed conspicuous ability. While still an undergraduate, he undertook with his teacher, Dr. J. H. Pratt, the solution of a bacteriological problem relating to typhoid fever, and this was published the month that he graduated, in the *Journal of the American Medical Association*. Thus he began the practice of investigation and publication, which he continued to the very end of his life. He received the degree of Doctor of Medicine in 1907, and the following year he served as interne in the Massachusetts General Hospital.

Thus far he had followed the beaten path. But now he departed from the course which at that time was almost universal in America. Instead of entering at once on the practice of his profession, he undertook his "Wander Jahre," a custom which, earlier at least, was frowned upon in America, but which in Europe has for centuries been held to offer the greatest rewards to the student in search of an education.

He spent two years in the Johns Hopkins Medical School at Baltimore, first as Assistant Resident Physician under Dr. Thayer, and later as Fellow in Pathology under Dr. Welch. In April of 1910, he went to Berlin and worked in the laboratory of Emil Fischer on organic chemistry. In the autumn, he returned to this country and

became Assistant Resident Physician in the Hospital of the Rockefeller Institute, then newly opened. He remained there for almost two years, leaving in the spring for another trip to Europe where he visited a number of clinics in Germany, made a short stay in Russia, and worked for six weeks on a physiological problem in the laboratory of Professor Krogh in Copenhagen.

He now returned to Boston after an absence of over four years. He did not return, however, with the idea that his education had been completed; that his student days were over. The Peter Bent Brigham Hospital had just been erected on ground adjacent to the Harvard Medical School, and it was intended that this hospital should be organized as a medical clinic of the school. Dr. Peabody was offered the position of Resident Physician and accepted this proposal for the reason, as he said, that this new institution provided facilities and equipment and teachers that would permit him to continue his studies and investigations under favorable conditions, and also because it gave him an opportunity to aid in the development of a modern medical clinic in which teaching and research should be important functions. At that time new ideas concerning medical education were in the air, and he was one of the small group of young men in this country who recognized the need of developing a scientific atmosphere in the medical clinic if the medical schools were to perform their proper function, and if medicine in this country was to keep abreast of that existing in other parts of the world.

He continued in residence at the Peter Bent Brigham Hospital for three years, working in the clinic, developing his ability as a teacher, busy in the wards, widening his experience with the maladies that afflict man, and increasing his sympathetic understanding of those who suffer, active in the laboratory, constantly carrying on investigations with methods of precision, and thus extending his knowledge of the nature of disease and increasing his power as a man of science. During all these years which had passed since graduation, he showed a remarkable spirit of restraint and patience by persisting in the course of training on which he had years before, voluntarily and independently resolved.

But these years were not merely years of self development and selfish acquisition of knowledge. He had been of great benefit to all the

patients who came under his care, he had been helpful to the students with whom he had been in contact, he had been useful to his university to which he was devoted, and he had been of service to humanity through the contributions he had already made to medical knowledge. But in still other ways he was of service, for in 1914 he was given leave of absence to join a commission of the Rockefeller Foundation which went to China to give advice regarding the new school of medicine which it was proposed to create in Peking. As the medical member of this commission, he undoubtedly had much influence in shaping the future policy of the Peking Union Medical School, and he was later made a member of the China Medical Board of the Rockefeller Foundation.

In 1915 he gave up his residence at The Peter Bent Brigham Hospital but continued as Physician to that institution, and was appointed Associate Professor of Medicine in Harvard University. He now continued for five years to teach, to practice, and to investigate. During these years, however, there were many other professional activities. In 1917 he served as a member of the American Red Cross Commission to Roumania, and later to Russia. On the entry of the United States into the war, he became a member of the Army Medical Corps and served in hospitals in this country, later going to France as Medical Consultant.

In 1921 he was appointed Professor of Medicine in Harvard University and, at the same time, became Director of the Thorndyke Memorial Laboratory. In Dr. Peabody's words, this laboratory "is a research department of the Boston City Hospital. Its establishment is due to the conviction of the Board of Trustees that the responsibility of the City Hospital is not limited to the treatment and care of individual patients, but includes also medical teaching, preventive medicine, and medical research." This attitude on the part of the authorities of this institution marked a decided departure from the traditional policy of American municipal hospitals, and was of much significance for future medical education in this country. It was very fitting that the Trustees should have turned to Dr. Peabody to undertake the direction of this new department. Brief mention can only be made here of the splendid manner in which he carried out the plans of its organization, arranging that its equipment should permit

the prosecution of fundamental studies concerning disease, and gathering together for its staff a group of well trained young men, eager for research. Here Dr Peabody continued his teaching and investigation, at the same time stimulating and aiding his co-workers. Within a short time important contributions from the staff began to appear.

Dr Peabody began his own career as an investigator of disease by undertaking studies concerning typhoid fever, the first of which has already been mentioned. During his residence at the Johns Hopkins Hospital, he began his studies of heart disease. Later, at the Rockefeller Institute, he undertook the investigation of problems relating to poliomyelitis and acute lobar pneumonia. At the Peter Bent Brigham Hospital, he began a long series of investigations concerning metabolism and the function of respiration. While Director of the Thorndyke Laboratory, he undertook the study of pernicious anemia. To all these subjects he made definite contributions. In all of his studies he was obviously interested in the application of the results to practice. For instance, he made studies concerning the function of respiration which have much scientific interest and significance, and he then indicated the application of his results, he showed the importance of a decrease in the vital capacity of the lungs as a factor in the production of dyspnea in heart disease, and demonstrated how the determination of the vital capacity could be made without difficulty in patients. He thus introduced into clinical medicine a new method that has proved to be of distinct value.

limited extent as practitioner, he found time to respond to many demands that were made upon him to give aid and council in projects of importance to medicine. When the Journal of Clinical Investigation was founded in 1924, he was made a member of the Editorial Board. His interest in, and sympathy with, the young men of the medical clinics who were making original contributions to the science of medicine, made him keenly desire that a special organ should be established in which their reports might be published. He was an active and useful member of the Board, and helped in shaping its policies. He served on the Council of the Association of American Physicians, and was also an officer in this organization. In 1926 he was made a member of the Board of Scientific Directors of the Rockefeller Institute for Medical Research.

His ability and training, his upright character, his academic interests, his success as a teacher and investigator, made him sought after by a number of universities to undertake the reorganization of their departments of medicine along modern lines. He refused, however, to leave his own university, believing that here he could be of the greatest service.

At the age of forty-five, he was at the height of his usefulness. With an ideal training, full of energy and resourcefulness, all those who were interested in medicine and its future looked upon him as one of its most able representatives, and as one upon whom would fall many of the responsibilities associated with shaping the development of medical education and practice in this country during the next decades. When, therefore, in the summer of 1926 his friends heard that, although apparently in the best of health, he was stricken with a serious disease, from which there was little chance of his recovering, they were shocked and dismayed, shocked that they were soon to lose a beloved associate, dismayed that the profession of medicine was to lose one of its most able defenders and promoters. But no consternation or apprehension was evident in Dr. Peabody himself. With at least an outward calmness and tranquility, he faced the inevitable. He decided not to let the knowledge of his fate hinder him from continuing his work or prevent him from leading his accustomed life. Consideration for his family and friends undoubtedly influenced him in coming to this decision. Not with a sad and sorrowful countenance, but with

a bright and unflinching spirit he continued his daily tasks. For over a year he continued his work, a comfort to his patients, an inspiration to his students and associates, a champion of the science of medicine, and an instrument in promoting its progress.

He was not only interested in the development of the science of medicine, however, he understood that "the application of the principles of science to the diagnosis and treatment of disease is only one limited aspect of medical practice." Shortly before his death he wrote an essay on "The Care of the Patient," which not only is a beautiful example of simple, straightforward writing but is an exposition of his own attitude toward his fellow men. The essay closes with the effective lines, "One of the essential qualities of the physician is interest in humanity for the secret of the care of the patient is in caring for the patient." And this is also one of the secrets of his own engaging personality. This Abou Ben Adhem was devoted to his friends, fond of his associates. He liked people. He had delightful social qualities and concealed a seriousness of mind and a great earnestness of purpose under a delightful and winning humor. He was always—

"A square-set man and honest, and his eyes,
An out-door sign of all the warmth within,"

and even during his last days—

"Smiled with his lips—a smile beneath a cloud"

Through the death of Dr. Peabody, American medicine has lost one of its most able representatives, the American Society for Clinical Investigation has lost one of its most valuable members, and this JOURNAL has lost one of its most important contributors. But his life and death were precious things which all of us, and especially the young men entering the profession, cannot treasure too highly.

RELATIONSHIP OF ACUTE INFECTIONS TO GLOMERULAR NEPHRITIS¹

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The etiological relationship of infections to the diffuse form of acute and subacute nephritis is a problem which for many years has commanded attention, but has rarely received more than casuistic study.

Löhlein (a) in 1907 described in detail the early lesions of the glomeruli in acute glomerular nephritis, as well as the subsequent changes that took place in the kidney during the subacute and chronic stages of the disease. Since a large proportion of his cases of acute and subacute nephritis occurred in patients suffering from various forms of infection, usually due to streptococci, he concluded that in the vast majority of cases acute glomerular nephritis was the direct result of streptococcus infection. Fahr (1912), somewhat later, pointed out the frequency with which acute glomerular nephritis was preceded or accompanied by infections particularly those due to streptococci, while Volhard and Fahr (1914) state that in their collected cases one quarter of all those nephritides associated with infections followed tonsillitis, and almost three quarters, 125 of 179, were connected with infections of the upper respiratory tract. Of a total of 67 cases of acute diffuse glomerular nephritis, 44 suffered from angina, scarlatina, wound infections or erysipelas. In general most of the statistical evidence that can be obtained (Hill (1919), Bell and Hartzell (1922), Kuczynski (1919a), Stolz (1925), Blackfan (1926)) tends to confirm the fact that streptococcus infections and especially tonsillitis precede directly or accompany the onset of a considerable number of cases of acute diffuse glomerular nephritis. Infections due to other or-

¹ Aided by a grant from the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation

² Jacques Loeb Fellow in Medicine

ganisms, such as the pneumococcus, are also recorded in this relationship, but as compared to scarlatina and other streptococcus infections they are comparatively infrequent.

A number of observers, however, including Munk (1916a and b) have not been inclined to accord much importance to the streptococcus, or other known bacteria, in the etiology of acute nephritis. Though recognizing the close relationship that is often found to exist between glomerular nephritis and many forms of streptococcus infection they consider the actual cause of this form of nephritis unknown.

Attempts to produce glomerular nephritis in animals by the injection of streptococci have been only partially successful. Ophuls (1917), who upholds the infectious origin of glomerular nephritis, reports the production of glomerular lesions in 14 of 48 rabbits injected intravenously with cultures of streptococci. Kuczyński (a) made repeated injections of streptococci into mice and believed that by this method he could produce glomerular lesions similar to those observed in man. Bell, Clawson and Hartzell (1925) report the results of repeated injections of hemolytic and non-hemolytic streptococci in 14 monkeys. In two animals there developed a severe nephrosis, in one an interstitial nephritis, while in one monkey injected repeatedly with cultures of *Streptococcus viridans*, there occurred an acute glomerular nephritis. Duval and Hibbard (1926) state that they can produce injury to glomeruli in rabbits by the injection of certain lytic products of *Streptococcus scarlatinae*.

inflammation, it has been the idea of other observers (Schridde (1913)) that the diffuse lesions in the glomeruli are caused by the elimination of a toxin, produced by streptococci or by other bacteria in a focus of infection distant from the kidney

The demonstration by Dochez (1924) and by Dick and Dick (1921a) that a type of hemolytic streptococcus is the cause of scarlet fever adds fresh incentive to investigations on this problem, for the post scarlatinal nephritis has always been considered as the prototype of the diffuse glomerular variety. The experiments, moreover, of Dick and Dick (1924b) on the elaboration of a filterable "toxin" by *Streptococcus scarlatinae* indicate still further methods which might be applicable to studies upon nephritis

It has seemed to us important to investigate two phases of the problem, first the relationship of acute infections to the onset of glomerular nephritis, and secondly the relation of infections to the progress of nephritis. If streptococcus infections of the upper respiratory tract, such as tonsillitis, sinusitis, etc., are directly responsible for the onset of glomerular nephritis, the progress of the disease might bear some relationship to the course of the infection. With the subsidence of the infection and disappearance of the infecting organism one might expect recovery from the nephritis, provided the kidney itself is not the seat of active bacterial growth, while progression of the nephritis to a subacute or chronic stage might be accompanied by persistence or exacerbations of the infection such as those of the upper respiratory tract, or at least by the continued presence of the infecting organism in these situations

With this idea in mind it has been possible to study forty cases of acute or subacute glomerular nephritis in young adults, and in twenty-seven of these to follow the course of the disease with some care over a period varying from a few months to four years. Cases of focal nephritis occurring in bacterial endocarditis were excluded

The ages of the patients were as shown on page 4

Most patients were seen within a few days to a few weeks of the apparent onset of their disease while a few developed the disease under observation. Daily variations in the clinical course of the disease were recorded with daily observations of the urine and blood pressure, frequent examination of the fundus oculi, and repeated determinations

of renal function. Cultures were made from any obvious infection. The accessory nasal sinuses were always examined, and we are greatly indebted to Dr. Crowe and his staff for their assistance in this connection, and for the operative procedures which they have performed on these patients. When it was not possible to detect an obvious acute infection after a careful search, cultures were made by the swab method from the tonsils, pharynx and naso-pharynx, and from the tonsils by the pipette method used by Bloomfield and Felty (1923). Cultures were repeated during the course of the disease, during convalescence and after recovery. The swab method was employed to obtain cultures from the pharynx and fauces of the patients who were tonsillectomized. The urine from patients during the acute and subacute stages of the disease was cultured in amounts of 1 cc

Age of patients

Age	Number
1-10	1
10-20	14
20-30	14
30-35	5
35-	6
	40

onset of acute nephritis Tonsillitis occurred in almost 53 per cent of the cases, while infections of the accessory nasal sinuses, throat and respiratory tract taken together were found in 85 per cent It is also obvious that hemolytic streptococci prevail as a cause of these infections, since they occurred in 81.2 per cent of the infections studied bacteriologically

The time interval between the onset of the acute infection and the onset of the nephritis varied considerably in the different cases and could not always be definitely determined. In one case (IV) recurring infections probably due to hemolytic streptococci of β type had preceded the apparent onset of nephritis for three months In another case infection of the tonsils and antra due to hemolytic streptococci had been almost continuous for three months when the patient developed acute nephritis while under observation In other cases

TABLE 1
Incidence of acute infections at onset of 40 cases of acute and subacute nephritis

Number of cases	Infections present		Infections absent	
	Number	Per cent	Number	Per cent
40	34	85	6	15

the apparent interval was not more than ten days and in some cases the infection was unrecognized by the patient and was first discovered at the physical examination

In order to investigate the second phase of this problem an attempt was made to study these patients more or less continuously over long periods of time This has been accomplished with considerable success in 27 of the 34 patients in whom the onset of acute nephritis was directly preceded or accompanied by an acute infection

These 27 cases have been divided into two groups, first those who, as far as can be determined, have recovered from the attack of acute nephritis, and secondly, those who still show evidence of nephritis, or in whom the disease has definitely progressed or has terminated fatally

In the first group there were 14 patients, 9 of whom had an acute tonsillitis due in 5 instances to hemolytic streptococci of β type, and in one to streptococci of α type. In two instances cultures were not

made during the acute attack. One patient had acute tonsillitis associated with broncho-pneumonia due to hemolytic streptococci of β type, two patients had broncho-pneumonia due to hemolytic streptococci, and two patient sinusitis, one due to hemolytic streptococci

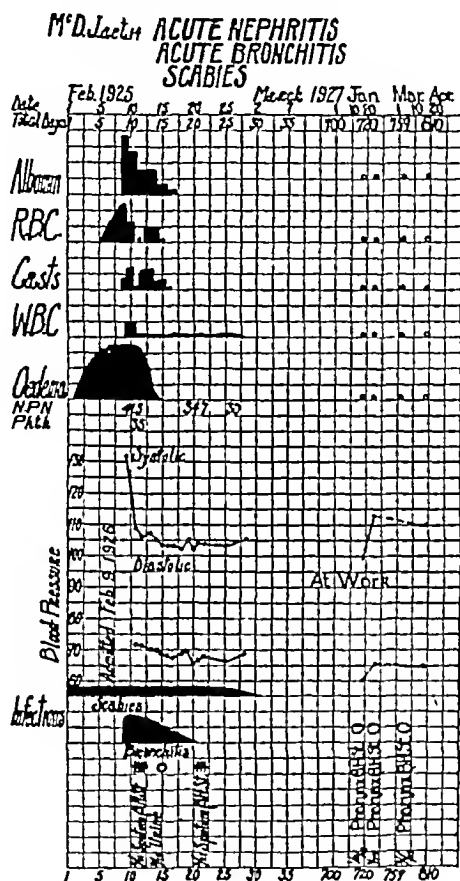


CHART I Case I, showing the results of urinary examinations, the degree of edema, the non-protein nitrogen of blood, and phthalein excretion, the changes in systolic and diastolic blood pressure, the duration of infections and the results of bacteriological examinations charted chronologically

of β type and one to Pneumococcus type IV. In seven of the cases of tonsillitis, tonsillectomy was performed. In two of these the excised tonsils were obtained for culture and showed a pure growth of hemolytic streptococci. In the two cases of sinusitis, cultures were

obtained from the antra and the ethmoidal sinuses at operation. The following abstracts and charts indicate the course of the disease and the results of repeated cultures in four cases of this group.

Case I McD J, male, white, aet. 14. Admitted to the Johns Hopkins Hospital February 9, 1925, complaining of bad cold and kidney "trouble." He had had measles, mumps and nasal operation at 4. Three attacks of tonsillitis in 2 years. Two weeks before admission developed scabies, one week before admission swelling of face, anorexia, vertigo and vomiting. A few days before admission voided bloody urine. Examination showed slight pallor, moderate edema about the eyes and face and over shins, scabies, numerous râles throughout both lungs. Heart and abdomen normal. Blood pressure 132/95. Temperature 99.5°. Pulse 90. Albuminuria, hematuria, and cylindruria. Hemoglobin 62 per cent. Red blood cells 3,280,000, white blood cells 6,800. Wassermann reaction negative. X-ray of chest showed "extensive shadows through both lungs." February 11, culture of sputum showed great numbers of hemolytic streptococci of β type. By February 12 the edema had disappeared, râles still persisted in the chest, cultures of the urine showed no growth. On February 21 cultures of sputum showed hemolytic streptococci still predominating. Discharged March 4. Has remained well for 2 years. During January, February and April 1927, physical examination showed nothing abnormal, the urine has been normal, the blood pressure 110/70 and cultures from the pharynx have not shown hemolytic streptococci of β type. Chart I.

Summary A mild case of acute nephritis in a boy of 14 suffering from broncho-pneumonia due to hemolytic streptococci of β type. There was edema of the face, transient slight hypertension, albuminuria, hematuria, cylindruria, with some increase in blood non-protein nitrogen and decrease in phthalein excretion. Rapid recovery. In good health for 2 years and 3 months after attack, with normal urine, normal blood pressure, and pharynx and tonsils free from hemolytic streptococci of β type.

Case II L S, male, white, single, aet. 21, printer. Admitted to the Johns Hopkins Hospital February 26, 1926 complaining of bloody urine. Measles, mumps and pertussis, broncho-pneumonia at 12, tonsillitis at 17. Urethral discharge for 2 months. No scarlet fever or diphtheria. Severe sore throat from December 26, 1925 to January 3, 1926, hematuria with nausea and vomiting during first week in January, for three weeks before admission swelling of face and feet. Examination showed edema of face, swollen red tonsils, enlargement of submaxillary lymph nodes, normal fundi, moderate hypertension (140/90), albuminuria, hematuria, cylindruria. Hemoglobin 85 per cent, red blood cells

5,440,000, white blood cells 10,040, Wassermann reaction negative, Temperature 98.6° Culture from tonsils shows hemolytic streptococci of β type By February 10 general improvement, less edema, right fundus shows two small patches of exudate During following week rapid improvement February 17 tonsillectomy, cultures from excised tonsils give pure growth of hemolytic streptococci of β type February 2, temperature 102.6°, throat very sore February 22, white blood cells 17,520, February 24 return of edema, increase in red blood cells in urine, infection of right nostril and purulent discharge, culture from nasal discharge gives hemolytic streptococci of β type, February 28 improved, edema

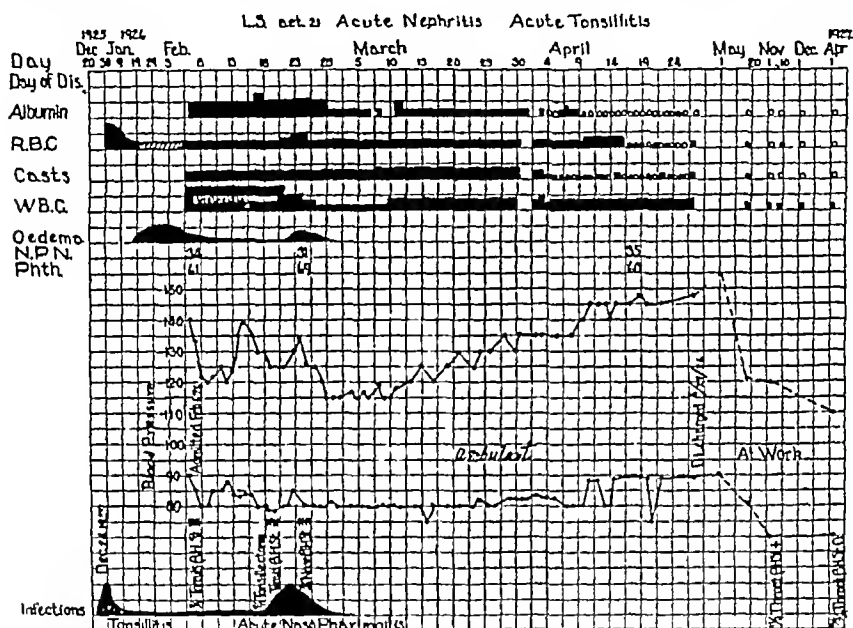


CHART II Case II, showing the results of urine examinations, the non-protein nitrogen of blood and phthalein excretion, the changes in systolic and diastolic blood pressure, the bacteriological examinations and course of the infection charted chronologically

disappeared, discharge from nostril diminished, temperature has gradually fallen to 100°, white blood cells 11,120 Continuous improvement until discharge April 27 with no edema, blood pressure 128/80 and no albumin, red blood cells or casts in urine After discharge the blood pressure rose temporarily though patient felt well, and urine was normal Examinations made in November and December 1926 and in April 1927 have shown the patient to be normal The blood pressure has been 120/70, the urine has not shown albumin, red blood cells or casts Cultures from the throat have not shown hemolytic streptococci, since November 9, 1926 Chart II

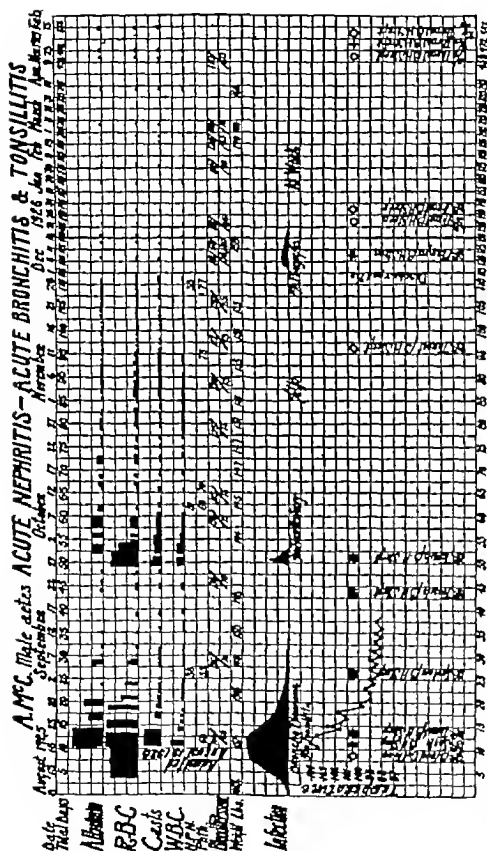


CHART III Case III, showing the results of urine examinations, the non protein nitrogen of blood and phthalen excretion, the blood pressure, weight, the course of infections, the temperature and results of bacteriological examinations charted chronologically

Summary A case of acute nephritis in a young white man with acute tonsillitis due to hemolytic streptococci of β type, moderate edema, hypertension, albuminuria, hematuria and cylindruria, transient changes in fundi. Normal blood non-protein nitrogen and phthalein excretion, rapid improvement. Tonsillectomy followed by infection of naso-pharynx and nares by hemolytic streptococci of β type with exacerbation of nephritis. Transient elevation of blood pressure after discharge with eventual recovery. In good health one year after attack with normal urine and blood pressure and no growth of hemolytic streptococci of β type in pharyngeal cultures.

Case III A McC, male, white, married, aet 23, painter. Admitted to Johns Hopkins Hospital August 19, 1925 complaining of pain in chest. He had pneumonia at 2, measles, mumps and pertussis as a child, and frequent colds. Ten days before admission epigastric pain, frequent cough, with dark urine for 6 days. Examination showed temperature 102° , pulse 96, aspirations 32. Acutely ill, enlargement of tonsils, no facial or subcutaneous edema, signs of partial solidification of right upper lobe. Blood pressure 110/60, albuminuria, hematuria, cylindruria, white blood cells 17,000. August 2, cultures from sputum show hemolytic streptococci of β type, no pneumococci, blood cultures negative. August 21, continuous fever from 101.8° to 103.6° , tonsils acutely swollen, cultures give hemolytic streptococci of β type. August 25 patient much improved. Temperature 99° to 101° . Urine culture shows no growth. September 28 throat and tonsils swollen, pain in back, gross hematuria. September 29 tonsillectomy, cultures from tonsils give profuse growth of hemolytic streptococci of β type. October 7, fundi normal, slow convalescence. October 14, urine culture gave no growth. November 28 discharged much improved. December 8, mild pharyngitis, otherwise well, cultures from pharynx show hemolytic streptococci of β type. Has remained well for 18 months. The blood pressure has been normal, the urine free from albumin, casts and red blood cells, cultures from the pharynx have not shown hemolytic streptococci since December 1925, except on one occasion when they were present in small numbers. Chart III.

Summary A case of acute nephritis in a young white man suffering from acute broncho-pneumonia and chronic tonsillitis due to hemolytic streptococci. No edema or hypertension, blood non-protein nitrogen and phthalein excretion normal, albuminuria, hematuria and cylindruria. Acute tonsillitis due to hemolytic streptococci of β type during convalescence with exacerbation of nephritis. Tonsillectomy. Gradual disappearance of blood and albumin from urine. Recovered and in excellent health $1\frac{1}{2}$ years after attack with normal

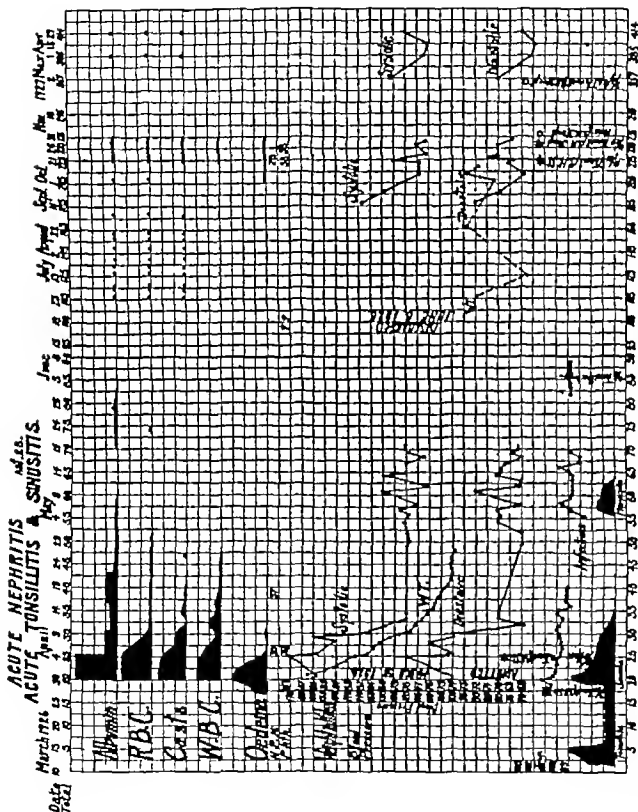


CHART IV Case IV C T, showing the results of urine examinations, the degree of edema, the non protein nitrogen of blood and phthalein excretion, the changes in systolic and diastolic blood pressure, the changes in weight and temperature, the results of bacteriological examinations and the course of infections charted chronologically

urine and blood pressure Repeated cultures from pharynx show no hemolytic streptococci of β type

Case IV C T, female, white, single, aet 28 Admitted to the Johns Hopkins Hospital March 3, 1926 complaining of swelling about eyes Measles during childhood, diphtheria in 1916, tonsillitis in 1917, 1920, 1921 and 1922 No scarlatina, numerous attacks of coryza In January 1926 severe cold for 3 weeks March 11, sore throat with chill, headache, nausea and vomiting, recovery in 6 days March 26, swelling of eyes with morning nausea, continuing to admission Examination showed anasarca, scarred tonsils, tender submaxillary nodes, purulent infection of right antrum, lungs normal, cardiac impulse forceful, reduplication of first sound at apex Blood pressure 160/100 Fundi normal Albuminuria, cylindruria and hematuria Temperature 100°, Pulse 100, Hemoglobin 74 per cent, red blood cells 3,872,000, white blood cells 8,400, cultures from tonsils show hemolytic streptococci of β type, cultures from urine no growth April 1, right antrum irrigated, anasarca decreased Temperature 99.4° to 100° April 5 culture from nostrils give hemolytic streptococci of β type April 13 infection healed, temperature normal, no edema, urine contains traces of albumin, occasional hyaline cast and white blood cells June 3, tonsillectomy followed by uneventful recovery Patient has remained well with normal urine and blood pressure (110/64-126/80) to May 1927 Cultures from pharynx on October 21, 1926 and October 28, 1926 still showed moderate numbers of hemolytic streptococci of β type Cultures from the pharynx on March 2, 1927 showed no hemolytic streptococci Chart IV

Summary A case of acute nephritis in a young white woman, preceded by acute tonsillitis and accompanied by sinusitis due to hemolytic streptococci of β type, anasarca, hypertension, albuminuria, hematuria and cylindruria, normal non-protein nitrogen and phthalein excretion Drainage of sinuses Recovery from the infection and rapid convalescence from nephritis Tonsillectomy In excellent health one year later Urine and blood pressure normal Cultures from pharynx 4 months after attack still showed hemolytic streptococci of β type Cultures from pharynx after one year showed no hemolytic streptococci

The preceding protocols and charts illustrate the course of the disease as it occurred in 10 of the 14 cases that have apparently recovered from the attack of acute nephritis Four of the 14 cases report themselves as being well, but have not been properly studied since recovery Of the ten cases that have been carefully studied, nine or 90 per cent are free from infections of the upper respiratory

tract one to four years after the attacks of nephritis, and cultures have shown that the fauces and nasopharynx are free of the organisms originally producing the infection. One of the ten patients has remained a carrier of hemolytic streptococci of β type.

During the convalescence from the disease in this group of patients, the mild exacerbations of nephritis, so frequently described, were observed in several. These are illustrated in the charts of cases II and III. They were observed to accompany a recrudescence or an extension of the infection. One patient suffered four such exacerbations of nephritis during a period of six months. Each exacerbation was related directly to the recurrence of a mild attack of tonsillitis due to hemolytic streptococci of β type. Removal of the tonsils has been followed by apparent recovery.

There is an obvious criticism of the results recorded in this group of patients. It may be argued, as Addis has done, that in spite of the excellent health of these individuals the nephritis remains latent, unrecognizable by ordinary methods, but slowly progressive. In order to detect abnormal elements in the urinary sediment in such patients Addis has devised a concentration test and believes by this means that it is possible to recognize a latent stage of the disease which may be present for years. We have not had an opportunity to employ this test except in one or two instances, but on these occasions the urinary sediment could not be differentiated from that of normal persons. In other respects, however, it has been possible to confirm in detail the changes that Addis has described as taking place in the character and numbers of the cells and casts of the urinary sediment during the subsidence of the acute stage of the disease, or during the progression of the acute to the chronic or terminal stage. It may be said, however, that by the usual methods of examination it has not been possible to detect evidence of disease in these patients who have apparently recovered. Moreover the contrast between this group and the following is so great that there seems justification in making a sharp distinction between them.

The second group consists of 13 patients whose disease progressed to a chronic stage or to a fatal termination. The same means were employed when possible to eradicate the infection in these patients as in the first group. One case of post scarlatinal nephritis with all

the evidences of chronic nephritis could not be followed carefully but is still living one year after the attack of scarlet fever. Of the remaining 12 cases, 4 had tonsillitis due to hemolytic streptococci of β type, 3 had tonsillitis and sinusitis in one case due to hemolytic streptococci of β type and in 2 cases due to streptococci of α type, 2 had

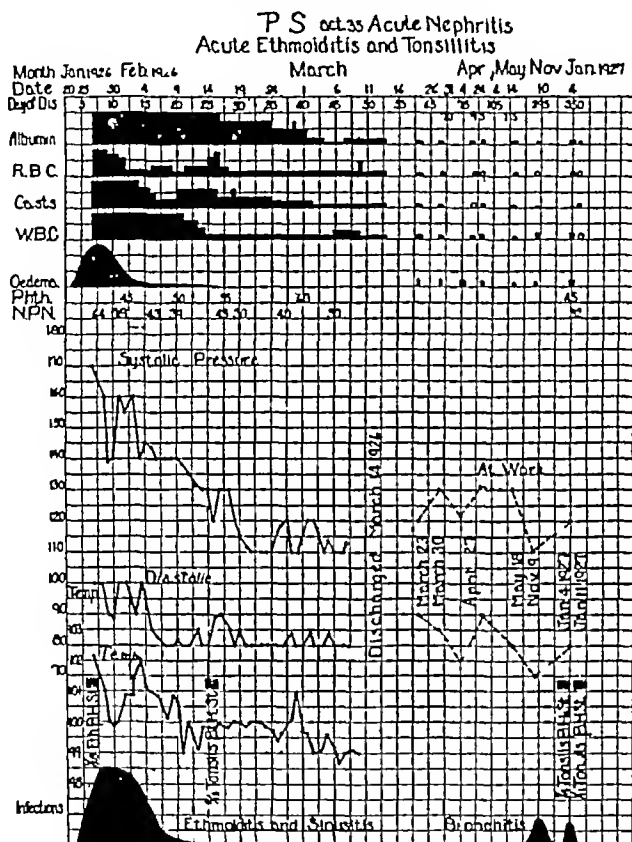


CHART V Case V, showing the results of urine examinations, the course of edema, the phthalein excretion and non-protein nitrogen of the blood, the changes in systolic and diastolic blood pressure, the temperature curve, the results of bacteriological examinations and the course of infections charted chronologically

sinusitis due to hemolytic streptococci of β type, one had tonsillitis due to hemolytic streptococci of β type combined with cystitis due to gonococci, and one had broncho-pneumonia the cause of which was not clear. Death occurred in this last patient, as well as in the patient suffering from gonococcal cystitis and in one case of sphenoiditis due

to hemolytic streptococci. Autopsy obtained in the first two cases showed acute and subacute diffuse glomerular nephritis.

Tonsillectomy and adenoidectomy was performed in six cases. In two of these, operations upon infected sinuses were also performed. In three cases the accessory nasal sinuses were punctured and drained. One patient refused tonsillectomy.

The following protocols and charts are examples of the changes observed during the course of the disease, and give the results of bacteriological examinations in this second group of 13 patients.

Case V P S, male, white, aet 35, mill worker. Admitted to the Johns Hopkins Hospital January 27, 1926 complaining of swelling of body. Pneumonia three times before age of 7, double otitis media in childhood, no scarlatina or diphtheria. On January 23rd, sudden swelling of eyes, face and feet, temperature of 102.5°, cough, epistaxis, discharge from nose, dyspnea, weakness and suppression of urine. Examination showed anasarca, subconjunctival hemorrhage on right, reddened pharynx, purulent discharge from ethmoidal regions, numerous râles throughout lungs, heart normal, blood pressure 180/100, acute urethritis, small quantities of dark urine with albuminuria, hematuria and cylindruria. Hemoglobin 85 per cent, red blood cells 5,510,000, white blood cells 11,800, increase in blood non protein nitrogen to 78 mgm. per 100 cc. Cultures from ethmoidal region show hemolytic streptococci of β type. January 28 blood culture no growth, temperature 102.6°, pulse 110. Antra irrigated, sinuses drained. Fundi show edema of retina, blurring of disc margins and enlargement of veins. Rapid improvement after February 4 with diuresis and disappearance of edema, fall in blood pressure, subsidence of sinus infection, fall in temperature to normal by February 10, reduction in blood non protein nitrogen to normal. Discharged March 14 in excellent condition, without edema, blood pressure 120/80, and without physical abnormalities except for slight albuminuria and the occasional presence of red blood cells, casts and many white blood cells in the urine. In November 1926 and January 1927, one year after the attack, occasional edema of the feet, slight albuminuria and cylindruria persist. Cultures from tonsils show many hemolytic streptococci of β type. Chart V.

Summary A case of acute nephritis in a white man associated with acute tonsillitis and sinusitis due to hemolytic streptococci of β type. Fever, anasarca, hypertension, albuminuria, hematuria and cylindruria with increase in non protein nitrogen of the blood and slight reduction of phthalein excretion. Rapid improvement. Refused tonsillectomy, persistence for one year of occasional edema of feet with mild albuminuria and cylindruria. Cultures from tonsils continue to show hemolytic streptococci of β type in considerable numbers.

Case VI J S, male, white, married, stevedore Admitted to the Johns Hopkins Hospital January 2, 1926 complaining of swelling of ankles and face No scarlatina, tonsillitis or diphtheria Three years ago some swelling of body for two weeks Two months ago swelling of feet gradually increasing to whole body, occasional cough and headache, vomited once Examination showed anasarca with fluid in pleura and peritoneal cavities, edema of retina, enlargement of ton-

J S act. Subacute Nephritis - Sinusitis and Ethmoiditis

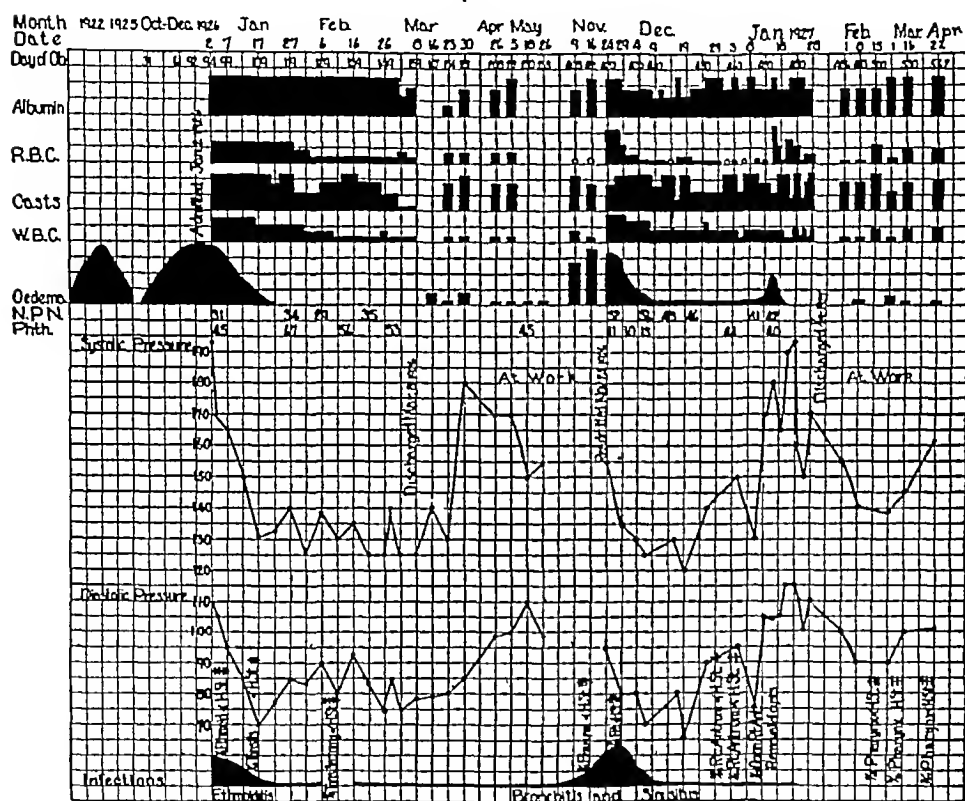


CHART VI Case VI, showing the results of urine examinations, the changes in edema, the non-protein nitrogen of blood and phthalein excretion the changes in blood pressure, the results of bacteriological examinations with course of infections charted chronologically

sils, some widening of cardiac dulness Point of maximum intensity 12 cm to left in 5th space, heart sounds clear Blood pressure 195/110 Muco-purulent discharge from ethmoidal regions Temperature normal Hemoglobin 62 per cent, red blood cells 3,160,000, white blood cells 9,800 Wassermann reaction negative Cultures from ethmoidal regions give pure growth of streptococci of α type Rapid improvement with disappearance of edema by January 26 Fundi

show perivasculitis and compression of veins by arteries. February 9 tonsillectomy. Discharged February 21 without edema. During next two months gradual return of edema, persistent moderate hypertension, marked albuminuria, cylindruria and occasional hematuria. Cultures from pharynx show great numbers of streptococci of α type. Readmitted November 24th with acute exacerbation of nephritis. There was pallor, anasarca, congestion and edema of nasopharynx, few râles over left upper chest. Increased blood pressure (156/94), retinal edema and perivasculitis, albuminuria, hematuria, cylindruria. Hemoglobin 75 per cent, red blood cells 3,100,000, white blood cells 9,000, Phthalein 10 per cent. Cultures from pharynx show great numbers of streptococci of α type. Cultures from urine no growth. By January 6, 1927 there was great improvement with almost complete disappearance of edema, decrease in retinal perivasculitis and hematuria. X-ray showed polyp in right antrum. January 13, 1927 radical antrum operation by Dr. Crowe followed by recurrence of anasarca, increased hematuria and rise in blood pressure to 168/104. By January 28, 1927 much improved, condition practically the same as before operation. Since discharge has felt much better than for a year. Slight pretibial edema, some increase in blood pressure with albuminuria and cylindruria persisting. Cultures from pharynx have shown repeatedly streptococci of α type. Chart VI.

Summary. A case of subacute nephritis in a young man progressing to a chronic stage with repeated acute exacerbations. The exacerbations were accompanied by acute attacks of tonsillitis and sinusitis. Cultures from the nasopharynx showed streptococci of α type in great numbers during both the acute exacerbations and quiescent periods. Hypertension and increase of blood non protein nitrogen, with decreased phthalein output during the acute attacks. Tonsillectomy with radical sinus operation one year later. Acute exacerbation of nephritis following latter operation with rapid improvement. Persistence of slight edema, albuminuria, cylindruria and hypertension, but general condition better than for a year.

Case VII. I. S., female white, aet. 15, student. Admitted to Johns Hopkins Hospital December 13, 1926, complaining of swelling of face and ankles for one year. Measles and varicella. No scarlatina or diphtheria. Tonsillitis in 1922 followed by tonsillectomy. Otitis media two years ago. Colds with fever every winter. In November 1925 some swelling of ankles. In January 1926, face, eyelids and neck swelled and was told she had kidney trouble. Since June recurrent swellings of face accompanied by sore throat. Examination showed slight puffiness of face and edema of feet, pallor, reddening of pharynx, acute adenoiditis, systolic murmur at apex, blood pressure 136/84, edema of retina, albuminuria, hematuria and cylindruria. Hemoglobin 78 per cent, red blood

cells 3 800 000, phthalein 55 per cent. Course in hospital characterized by many exacerbations of edema with increase in albuminuria and hematuria accompanied usually by fever, abdominal pain, leucocytosis of 13 000 to 17,000. One attack associated with acute otitis media and one attack with acute nasopharyngitis. Tonsillectomy and adenoidectomy. Cultures from excised adenoids and cultures made repeatedly from fauces and pharynx showed streptococci of α type in great numbers. Last seen May 31 1927 and showed slight pretibial edema, some tortuosity of retinal vessels. Heart dulness 9.5 cm. to left in 5th space, blood pressure 146/100, albuminuria, hematuria, cylindruria. May 11 culture from pharynx gave streptococci of α type. Chart VII.

Summary. A case of nephritis in a young girl, progressing from a subacute to chronic stage with exacerbations accompanied by recurring infections of adenoids, nasopharynx and middle ear caused by streptococci of α type. Exacerbations of nephritis characterized by slight anasarca, fever, increased albuminuria, hematuria, cylindruria and gradual increase in blood pressure. Tonsillectomy and adenoidectomy. Persistence of streptococci of α type in almost pure cultures in pharynx.

The features which distinguish this second group of cases from the first are the persistence of definite evidence of renal injury for a long period as illustrated by case V, or the actual progression of the disease to chronic nephritis as illustrated by cases VI and VII combined with a persistence of the original infection or of the infecting organism. A close correlation between these two conditions occurred in 10 or 83.3 per cent of 12 cases. Of the two remaining cases, one after tonsillectomy continued a carrier of hemolytic streptococci of β type for a year, when these organisms disappeared from the pharynx. Later an infected antrum was drained. From the pus influenza bacilli and streptococci of α type were obtained. In the second of these two cases the acute attack of nephritis was accompanied by an acute tonsillitis due to hemolytic streptococci of β type. For a year after tonsillectomy cultures from the pharynx have not yielded hemolytic streptococci, but the patient has shown a persistent increase in blood pressure with some cardiac hypertrophy.

When one compares the natural history of the disease in these two groups, it becomes apparent that there is a relatively close correlation between the occurrence and persistence of infections caused usually by hemolytic streptococci with the onset and progress of the nephritis.

Though infections due to hemolytic streptococci precede or accompany the onset of a large proportion of all cases, complete recovery from nephritis has rarely occurred unless the infection has been eliminated and the infecting organism has disappeared. Persistence or exacerbation of the infection with the continued presence of the organism has, on the other hand, been the rule in the cases that have progressed unfavorably.

It might be suggested that the difference in the course of the nephritis observed in these two groups depended in part or entirely upon

TABLE 2

Bacteriology of infections occurring at onset of 34 cases of acute and subacute glomerular nephritis

Form of infection	Number of cases	Bacteria present					No predominating bacteria	Cultured
		Strep Hemolytic β	Strep Hemolytic α	Pneumococci	Staph alb	Conococci		
Tonsillitis	15	11	2				1	
Tonsillitis and bronchitis	3	2					1	
Sinusitis	7	5	1	1				
Bronchitis, broncho pneumonia, otitis and adenoiditis	4	2	1		1?			
Scarlet fever	4	2					1	
Cystitis and pyelitis	1					1		
Total	34	22	4	1	1	1	3	

Of 32 cases cultured 22, or 68.7 per cent gave pure or predominating growth of hemolytic streptococci of β type and 4 or 12.2 per cent of α type.

severity of the initial acute attack of nephritis. It is probable that this has some bearing upon the rapidity with which convalescence may take place and may in occasional instances determine the ultimate recovery. But the attack of nephritis in some of the patients of the first group was quite severe, whereas the initial symptoms and acute phase of the nephritis in some of the patients in the second group were rather mild, and it does not seem likely, therefore, that a variation in the severity of the onset could in itself be responsible for so pronounced differences in the subsequent course as occurred in the two groups of cases.

The frequency with which recrudescences have occurred during the progress of the nephritis has been noticeable both amongst those patients that have recovered and those who so far have not. In the majority of instances these exacerbations were related chronologically to mild or severe recurrences of the infection. In many instances the only evidence of an exacerbation of the nephritis was the sudden increase in albumin, red blood cells, casts, leucocytes and epithelial cells in the urine, with a change in character of the cells and casts, and it is readily conceivable that an individual might be the subject of repeated exacerbations of this character without knowledge of them. One is tempted to suggest that this is a common mode of progress from the acute to the chronic stage of glomerular nephritis.

Though the facts collected suggest that the streptococcus producing the infection in these cases is also the cause of the nephritis, it is not possible to obtain actual proof for this contention. There has been no evidence to show that the streptococci gained entrance to the blood stream, or that they were eliminated in these cases through the kidney, for blood cultures in the febrile periods were always negative, and cultures from the urine in amounts of 1 cc. to 5 cc. have never, except in one instance, shown a growth of the organism encountered in the infections of the upper respiratory tract or elsewhere. The exception occurred in the patient with cystitis in whom the infection was due to the gonococcus.

It has frequently been suggested that the toxic substances produced locally by the streptococci and eliminated through the kidney might be the cause of glomerular nephritis following scarlatina and tonsillitis, and it has seemed to us a much more probable explanation than that the bodies of the bacteria themselves transported to the kidneys set up an inflammation of the glomeruli. In order to determine whether the types of streptococci isolated from these infections might produce "toxic filtrates" similar to those derived from streptococcus scarlatina, the various strains were grown in peptone broth at a pH of 7.4 for 18 hours, the cultures filtered through Berkefeld "N" filters and 0.1 cc. of the diluted filtrate tested by intradermal injection in susceptible persons. An area of erythema exceeding 1 cm. in diameter and appearing after 18 to 24 hours was termed a positive reaction. Filtrates prepared in the above manner from 18 hour growths of

14 strains including both types of streptococci isolated from these infections have all produced skin reactions in 1 to 100 dilutions or 0.001 cc. Many have given positive reactions in 0.0005 cc. and 0.0001 cc. and a few in 0.00005 cc. or even 0.00002 cc.

It has been shown by Trask and Blake (1924) that the urine collected from cases of scarlet fever during the acute phase of the illness contains a "toxin" possessing the properties of the toxic filtrate from the growth of *Streptococcus scarlatinae*. Similar results have been obtained by Birkhaug (1927) with the urine from cases of erysipelas. Attempts have been made to demonstrate the presence of "toxins" in the urines of our patients. Intense skin reactions have often been obtained with such urines, but as albuminous urines from patients other than those suffering from acute nephritis or from streptococcus infections have produced similar reactions, it is obvious that until technical difficulties, occasioned probably by the presence of coagulable protein are overcome, it is impossible to draw any conclusion as to the cause of the skin reaction.

It is undoubtedly important to classify as accurately as possible the strains of streptococci isolated from these infections, in order to determine whether any of them correspond immunologically to the more or less fixed strains of hemolytic streptococci of β type. Work is now in progress upon this problem.

SUMMARY

1 The onset of acute or subacute glomerular nephritis in 40 patients was preceded or accompanied in 85 per cent by an acute infection such as tonsillitis, sinusitis, broncho-pneumonia or scarlatina.

2 Cultures made from the infections in 32 cases showed hemolytic streptococci of β type in 68.7 per cent, and streptococci of α type in 12.2 per cent.

3 Ten cases among those that could be constantly observed recovered apparently from the attack of acute nephritis. In 9 of these, or 90 per cent, the infection and the infecting organism have disappeared.

4 Twelve cases among those that could be constantly observed progressed to a chronic stage or terminated fatally. In 10 of these, or 83.3 per cent, the infection or the infecting organism has persisted.

5 No evidence could be obtained, in this study, to show that the streptococcus caused the glomerular nephritis by actual invasion of the kidney, for blood cultures and urine cultures were negative

6 All the strains of the streptococci tested produced so-called "toxic filtrates," often of considerable potency and it seems possible that such "toxins" liberated by the growth of streptococci and eliminated through the kidney might cause glomerular nephritis in patients rendered highly susceptible in some way to these toxins

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ELLIPTICAL AND SICKLE SHAPED ERYTHROCYTES IN THE CIRCULATING BLOOD OF WHITE PERSONS

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INTRODUCTION

The normal erythrocyte is so uniform in shape that variations from the normal have been widely accepted as evidence of pathological conditions. Among the most striking of these variations are the changes in size and shape which occur in pernicious anemia. These variations do not, however, have any single characteristic type but are of almost unlimited diversification. On the other hand, there have been reported cases in which there were variations in the shape of the red blood cells which were wholly characteristic, and in which most of the abnormal cells were quite alike. The most important entity of this type is the so called sickle cell anemia, the first case of which was described by Herrick (1910). Numerous other cases have been described since then by Huck (1923), Sydenstricker (1924), and others, and in all of these cases the deformed erythrocytes have been, in general, quite similar. The characteristic type of the sickle cell is well known. Another type of erythrocyte is the oval type which has been especially prominent in the cases reported by Dresbach (1904, 1905), Bishop (1914), and by Huck and Bigelow (1923), respectively. The type of these cells can be seen in Bishop's illustration (fig 1). Finally, there have been seen, from time to time, long slender cells, especially in cases of secondary anemia. These cells have been noted in particular by Minot and Lee (see Plate V, preceding page 3, Nelson Loose leaf Living Medicine, Volume IV). Thus it would seem that the red blood cell, which under normal conditions maintains its biconcave shape with such remarkable regularity, is capable of being modified in shape in quite characteristic patterns. The exact nature

of the conditions producing these changes is not known, but a number of factors have been suggested as of etiological significance. Disorders of blood formation and the presence of abnormal substances in the serum have been suggested as possible causes of deformed red blood cells. Another important consideration with regard to etiology is the question of racial distribution. Pernicious anemia is much more common in the white race but has been reported in negroes. Sickle cell anemia has only been seen in negroes, and many observers have felt that, in this condition, the racial element was one of great significance. In addition to this racial distribution a familial distribution has been noted also, e g, sickle cells have been found with great regularity in the families of patients having typical sickle cell anemia. This finding of deformed erythrocytes in apparently normal individuals has opened up an important question as to whether the causative agent of the pathological conditions may not be, at least in part, a predisposition—in nature, racial or familial, or both. Cooley and Lee (1926) found sickle cells in '5 per cent of negro patients. Sydenstricker and his coworkers (1923) have stated that they have found latent sickling 13 times in examining over 300 negroes.

The present investigation resulted from the study of a case of moderate anemia in a white woman, characterized by the presence of numerous sickle and elongated erythrocytes. Unfortunately, this case was only studied for a very short time and many of the confirmatory examinations that would have been desirable were not obtained. However, the case was sufficiently marked to suggest examination of the patient's family. One sister, one brother and one niece were found to have both sickle and long, slender erythrocytes, while negative results were obtained in the blood of one brother and one sister. In addition to this case, five other white patients in the Vanderbilt Hospital (see table 1) have been found to have sickle or elliptical shaped erythrocytes, though in none of these have the cell changes been as marked as in the one case referred to above. These findings suggested the possibility that the deformed red blood cells seen in the patient referred to above, and in her relatives, might represent a mild form of sickle cell anemia or of some intermediary condition. Since the importance of the racial factor in this form of anemia had been stressed, and since the analysis of blood of normal

negroes had yielded the presence of sickle cells, the examination of a series of normal whites and negroes was undertaken to determine just what evidence of similarity or difference could be found in this regard. In brief, the results obtained indicate that in the case of normal individuals of the two races studied, there is very little difference, a slightly higher percentage of deformed cells having been found in the white than in the colored individuals in the cases examined.

REPORT OF CASE

Case 1 L B S The patient was an American born, white woman of Spanish and Scotch Irish descent, 32 years of age, who came into the hospital complaining of disability in walking. Her health had been very good until about ten months before entering the hospital. She had been troubled with soreness of the mouth, and bleeding about her teeth had occurred at times for several years. She had had hemorrhoids for about five years, these had bled once or twice every month, but not profusely. Her menses had been profuse, and usually lasted from seven to nine days. She was the mother of three children, the first of whom was still born, the other two were living and well, aged 14 and 10 years. Her present illness began about ten months before her admission to the hospital, with a respiratory infection which she thought was influenza. Following this infection she felt tired and weak at intervals for about three months. About four and one half months before admission to the hospital she noticed that she could not walk as well as before. She felt dizzy and there was some trembling.

Physical examination She was a pale undernourished white woman. Her temperature, pulse and respiration were normal. The mucous membranes were slightly pale. The head showed no abnormalities. The tonsils were moderately large and embedded. The neck presented no abnormality except that the posterior cervical lymph glands were palpable. The chest was symmetrical and the lungs presented no abnormalities. The heart showed no marked systolic shock. On percussion, the borders were outlined 2.5 cm. to the right and 8 cm. to the left in the fourth intercostal space. There was a soft systolic murmur at the apex, and in the second interspace on the left there was a loud blowing systolic murmur. At one time in this same area a loud diastolic murmur filling the whole of diastole and transmitted out toward the shoulder was heard. The rate and rhythm were normal. The blood pressure was 116/70. The abdomen was normal in contour. No areas of tenderness were found. The liver and spleen could not be felt. The extremities presented no abnormalities. There were no leg ulcers. On first standing, the patient fell backward to the right. After walking, she was steady with her feet together and there was only slight swaying on closing the eyes. When she was told that she was falling to the right, she did, and yet when support was withdrawn she steadied herself. When walking she was unsteady on turning when near the examiner, but when at the other end of the walk she was steady.

The finger to finger test was performed better with the eyes closed than with them opened, but here again, the right side was more at fault

The blood The red blood cell count was 3,850,000 per cubic millimeter The white blood count was 8,900 per cubic millimeter Hemoglobin 45 per cent (Sahlb) A smear stained by Wright's technique showed the red blood cells to have moderate achromia There was slight anisocytosis, the average size being normal There were some small cells but no very large ones There was rarely a cell that was polychromatophilic The most striking finding was the decided tendency of the erythrocytes toward sausage forms The platelets were apparently normal The differential count was polymorphonuclear neutrophiles 64 per cent, polymorphonuclear basophiles 1 per cent, lymphocytes 22 per cent, monocytes 12 per cent A fresh, sealed preparation was examined about one hour after it was taken, and the following findings were noted Most of the erythrocytes were fairly uniform in size Only a few small forms were seen and none of very large size From 5 to 10 per cent of the red blood cells were definitely sickle or sausage shaped, some having blunt and rounded ends, others having typical pointed ends All transitions from the typical sickle cell to the round normal erythrocyte were seen Many of the abnormal cells had slender processes, from 1 to 10 micra in length, which were obviously attached to the membrane of the cells These were more marked in the crescent forms, and in addition were in many instances seen free in the plasma The polymorphonuclear neutrophiles showed a definite increase in motility and contained numerous vacuoles, which showed in many instances a definite hemoglobin color In many of the leucocytes, both short and long rod-shaped structures were seen (some in the vacuoles mentioned above and some elsewhere in the cytoplasm) While these structures could not be identified absolutely as such, they seemed to be the long and short rods mentioned above, which had been broken off from the abnormal red blood cells No nucleated red cells or myelocytes were seen Many fragmented cells and shadow cells were present Figures 1, 2, and 3 show some of the characteristic findings in a stained blood preparation from this patient

It is of interest that one brother, one sister, and a niece of this patient gave evidence of the same peculiarities of the erythrocytes However, this phenomenon was not so marked among these individuals as it was in the patient It is unfortunate that ignorance and superstition on the part of the family prevented further study of the patient's blood and the examination of the blood of other members Figure 4 shows a sausage-shaped cell found in the blood of one of the patient's sisters The remaining five cases are grouped in table 1 Examination of this table shows that these patients represent a variety of pathological conditions and are of both sexes There does not seem to be any obvious relationship between these cases,

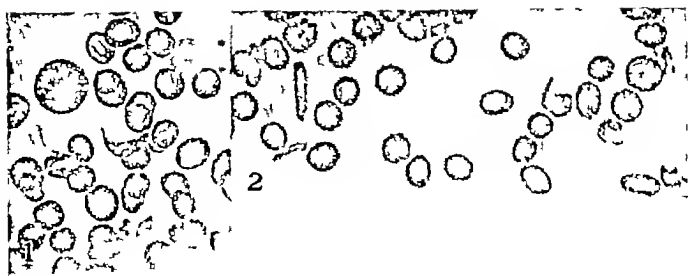


FIG 1 MICROPHOTOGRAPH OF A STAINED SMEAR OF THE BLOOD FROM CASE 1,
L B S $\times 600$

FIG 2 MICROPHOTOGRAPH OF A STAINED SMEAR OF THE BLOOD FROM CASE 1,
L B S $\times 600$

FIG 3 MICROPHOTOGRAPH OF A STAINED SMEAR OF THE BLOOD FROM CASE 1
L B S $\times 600$

FIG 4 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM ONE OF THE SISTERS OF CASE 1, L B S $\times 1000$

FIG 5 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM A L S (TABLE 1) $\times 1000$

FIG 6 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM W D A (TABLE 1) $\times 1000$

TABLE 1
White patients showing evidence of sickling phenomena

Initials and hospital number	Age	Sex	Chief complaint	Principal physical findings	Degree of sickling	Red blood cells per cubic millimeter	Hemoglobin per cent	White blood cells per cubic millimeter	Major diagnosis
A. L. S. No 2611 Figure 2	62	F	Inability to walk or to use right hand and arm	Right hemiplegia, palpable spleen, petechiae	Mild	3,855,000 to 4,570,000	50-65	2,500 to 6,500	Splenic anemia, hemiplegia
W. D. A. No 86 Figure 3	51	M	Dyspnea	Rheumatic heart in terminal stage, palpable spleen	Mild	5,200,000	82	13,450	Rheumatic heart disease
S. M. N. No 2697	19	F	Pain in right side of abdomen	Essentially negative	Very mild	4,130,000	77	3,900	Diagnosis unknown
J. K. P. No 3079	21	M	General glandular enlargement	General glandular enlargement, purpura, palpable spleen	Mild	3,800,000 to 2,690,000	55-64	126,000 to 525	Acute lymphocytic leukemia
E. V. No 3338	29	F	Diarrhea	Essentially negative	Mild	4,100,000	70	8,200	Diarrhea (cause unknown)

but the series is too small to be utilized for any general conclusion regarding the type of case in which such changes may occur. It is hoped that a larger series of hospital cases may be examined later with the object of determining whether these cells are found with any regularity in any particular clinical entities. Figure 5 represents one of the cells found in a fresh sealed preparation from A. L. S. Figure 6 shows a field in a fresh sealed blood preparation from W. D. A.

APPARENTLY NORMAL WHITE PEOPLE SHOWING CHANGES IN RED BLOOD CELLS (SUBJECTS 2, 3 and 4)

Since elliptical and sickle shaped erythrocytes were found to be definitely present in white patients it seemed advisable to extend this study to a series of normal white individuals. Accordingly, 102 normal white adults were examined. A comparative series of 98 negroes was studied also. The normal white subjects consisted of medical students of the Vanderbilt University Medical School, and thirteen nurses of the Vanderbilt Nursing School. Three subjects (subjects 2, 3 and 4) who showed elongated or sickle cells were found. In no case where these changes were found was a single observation relied upon, but many examinations were made at varying times with the same results on each observation.

Subject 2 M. C. The first of these individuals showing these characteristic cell changes was a white girl, 18 years of age, a student in the School of Nursing. She was in good general health. General physical examination was essentially negative. There was no generalized glandular enlargement. The spleen was not palpable and there was no discoloration of the sclerae. A fresh sealed preparation of whole blood on December 1, 1926, showed a number of sausage forms and slight filamentation without sickle shaped cells. Another fresh sealed preparation on December 2, 1926, showed a few sausage cells but no sickling and no filamentation. A third examination on January 25, 1927, revealed similar findings. On this date the other blood findings were: red blood cells 4,880,000 per cubic millimeter, white blood cells 12,500 per cubic millimeter, hemoglobin 75 per cent. A smear stained by Wright's technique at this time showed a small number of sausage forms. No very long cells, no filamentation and no changes in the staining reaction were seen. There were no abnormal variations in the size of the erythrocytes. The platelets were normal. Differential count: polymorphonuclear neutrophils 67 per cent, polymorphonuclear eosinophiles 5 per cent, polymorphonuclear basophiles 0 per cent, lymphocytes 25 per cent, monocytes 3 per cent. Figures 7 and 8 show the typical red blood cells seen in this subject. Figure 8 shows a sausage cell which has persisted even though crenation has occurred.

Subject 3 H B McS The second subject was a medical student, male, 21 years of age, who was in good health. His past history revealed no chronic illness, nor had he ever had jaundice. He had been feeling perfectly well. Nine years previously, for a day or two, his joints had been painful but without swelling or redness. There was no other history of joint symptoms. He had two sisters living and well. There was no history of serious illness among his relatives. Careful physical examination was essentially negative. There was no jaundice, the spleen was not palpable, and there was no general glandular enlargement.

The blood The red blood count was 4,970,000 per cubic millimeter. Hemoglobin 80 per cent (Sahl). Smear stained by Wright's technique showed the red blood cells to have normal staining characteristics. There was no achromia. Throughout the smear, at fairly frequent intervals, were definite pencil or sausage shaped cells, but these did not tend to be as long as the ones seen in the fresh preparation, the longest one being possibly a little less than twice the diameter of the average red blood cell. There was moderate but very definite filamentation. No true sickle cells were seen. The average size of the red blood cells was normal but rare microcytes were present. No macrocytes were seen. The platelets were normal. A fresh sealed preparation examined on November 29, 1926, showed fairly frequent sausage forms and a few definitely characteristic sickle cells. There was some filamentation. A second fresh sealed preparation was examined January 24, 1927, and at this time definite sausage forms were present in fair abundance. A few sickle cells were also seen. Moderate filamentation was present. On February 24, 1927, a fourth fresh preparation was examined with essentially the same findings as above. Icteric index was 6. Figure 9 illustrates the cells found in this subject.

Subject 4 J C McK The third individual in this series was a medical student 23 years of age. He was in good health. There was no history of jaundice nor was there any history of arthritic manifestations. Beginning on the third or fourth day after tonsillectomy, he had bled off and on for about one week. There was no history of bleeding at any other time, nor was there any history of bleeding in the family or among the relatives. The patient had been smoking somewhat excessively. Physical examination revealed irregular cardiac rhythm. In other respects the physical findings were not remarkable. The electrocardiograms showed ventricular premature contractions. This cardiac finding was apparently the result of excessive smoking.

The blood The red blood count was 5,200,000 per cubic millimeter. The white blood count was 8,600 per cubic millimeter. Hemoglobin 76 per cent (Sahl). A blood smear stained by Wright's technique showed sausage shaped cells here and there but no very long ones. There was a rare microcyte. The average size of the erythrocytes was normal. There was very slight filamentation. One typical sickle cell was seen. Another fresh sealed preparation on January 25, 1927, showed sausage cells at fairly frequent intervals, one sickle cell, but no

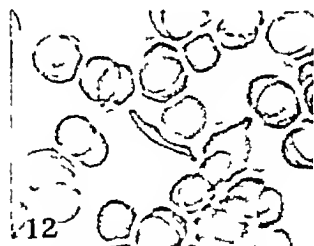
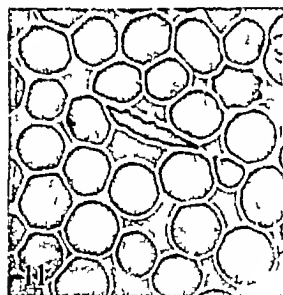
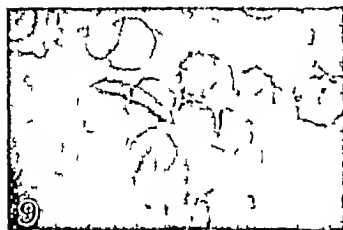
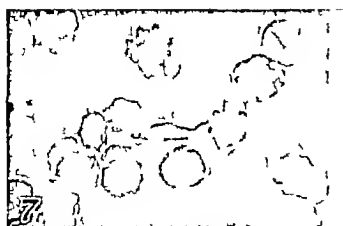


FIG 7 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM SUBJECT 2, M C. $\times 1000$

FIG 8 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM SUBJECT 2, M C $\times 800$

FIG 9 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM SUBJECT 3, H B MCS $\times 1000$

FIG 10 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM SUBJECT 4, J C McK $\times 1300$

FIG 11 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM W P (COLORED) $\times 1000$

FIG 12 MICROPHOTOGRAPH OF A FRESH SEALED PREPARATION OF THE BLOOD
FROM E W (COLORED) $\times 1000$

filamentation. A rare microcyte was seen. Another smear examined at the same time showed essentially the same findings. Icteric index was 4. Figure 10 shows the type of cell found in this subject.

Inasmuch as latent sickling had been well established in cases of sickle cell anemia by Emmel (1917), Sydenstricker, Mulherin and Houseal (1923), and Huck (1923), observations were made on a fresh sealed preparation from subject number 3 at intervals for over three days, and no true increase in the abnormal cells was found. The preparation was kept at room temperature. In subject number 4 there seemed to be some, but not marked increase, in the abnormal cells about 28 hours after the examination. This preparation was also kept at room temperature. There was nothing comparable in this respect, however, with the findings which have been reported in true sickle cell anemia.

Phagocytosis was looked for in two of these subjects (subjects 2 and 3) and none was noted. These preparations were examined on a warm stage with neutral red stain.

NEGROES SHOWING CHANGES IN RED BLOOD CELLS

The group of colored subjects consisted of Meharry Medical School students, 41, colored patients in Vanderbilt University Hospital, 50, colored employees in Vanderbilt University Hospital, 7, and colored visitors in Vanderbilt University Hospital, 2, a total of 100. Of these, five (four patients and one visitor) showed phenomena similar to those reported above for the normal white subjects. Two of the patients were carefully studied and their findings are reported in detail below. In the case of the other subjects it was impossible to make several examinations.

Colored patients showing sickling phenomena

One of these patients, W. P., was 44 years of age and had cardiac hypertrophy and myocardial failure as shown clinically and at the postmortem table. The second of these patients, E. W., was 45 years of age and was suffering principally from chronic bronchitis. She also had syphilis and hypertension.

The blood of W. P. A fresh sealed preparation examined February

18, 1927, showed one sickle cell and an occasional sausage form. There was mild filamentation. Another fresh sealed preparation was examined on February 24, 1927, and showed definite but not marked changes in the red blood cells. Two long narrow cells were seen, one of these being nearly three times as long as the average diameter of an erythrocyte. Other less pronounced sausage forms were observed. No true sickle cells were seen. There was mild filamentation. A smear stained by Wright's technique showed the red cells to be slightly achromic and an occasional cell basophilic. There was no stippling. The variations in size were normal except that there was a rare microcyte. There were no macrocytes. The principal variation in shape was toward the sausage forms. These were frequently found, were quite characteristic, and the longest were about twice the diameter of an average red blood cell. Two sickle cells were seen. There was mild filamentation. Platelets were normal. There was no evidence of phagocytosis. Red blood cell count 4,023,000 per cubic millimeter, white blood cell count 6,900 per cubic millimeter, hemoglobin 62 to 65 per cent. Icteric index 5. On February 28, 1927, a fresh sealed preparation, stained with neutral red and examined on a warm stage, showed active phagocytosis of the red blood cells by polymorphonuclear neutrophils but no phagocytosis by the monocytes. Figure 11 shows the type of elongated red blood cell found in this patient. Special examination was made for latent sickling as described by Emmel (1917), Sydenstricker (1924), and Huck (1923). No increase in the deformed erythrocytes was noted on the following day but on the second day they seemed to have increased, but not so strikingly as described in cases of sickle cell anemia.

The blood of E. W. A fresh sealed preparation examined on February 18, 1927, showed occasional sausage forms. No sickle cells were seen. There was mild filamentation. A similar preparation on February 24, 1927, gave similar findings. Red blood cell count 3,900,000 to 4,500,000 per cubic millimeter, white blood cell count 5,500 to 8,900 per cubic millimeter, hemoglobin 64 to 75 per cent. The blood Wassermann was positive. A stained smear showed slight achromia of the red blood cells. There was moderate basophilia. There were slight variations in size, the average red cell being normal in size. There were no microcytes. There were slight

variations in shape, the distinct tendency being toward mild sausage forms, which were found fairly frequently. There was mild filamentation. No stippling was present. No phagocytosis was found. No very long, slender sausage forms were seen but there was one which in length was about one and one-fourth times the diameter of the average red blood cell. The platelets were abundant. Reticulated count was two-tenths of one per cent. Icteric index was 3. On February 28, 1927, a fresh sealed preparation stained with neutral red showed both polymorphonuclear eosinophiles and neutrophils containing ingested red blood cells. Figure 12 illustrates typical red blood cells found in this case. Latent sickling was searched for in this case also and no evidence of this was found on either the first or second day after the preparation was made. There were frequent crenated, short, narrow cells on the day following the taking of the preparation and again on the third day.

Of the two other colored patients showing these peculiar cells, one had gonorrhea and the other had tuberculous peritonitis, pulmonary tuberculosis and congenital syphilis.

DISCUSSION

Since the report by Herrick (1910) many cases of sickle cell anemia have been observed and carefully studied. The data in the literature indicate that this disease is a definite clinical entity peculiar to the colored race. Sydenstricker and Huck have been especially active in the study of this disease and a full discussion of it may be found in their papers. From an analysis of the literature the principal demands for a diagnosis in so far as the blood is concerned are the following findings: (1) The presence of sickle shaped cells in varying numbers in fresh sealed preparations. (2) "Filamentation" of the red blood cells. (3) The presence of long narrow red blood cells in fresh sealed preparations. (4) Phagocytosis of red blood cells by mononuclear cells. The literature has been remarkably free from any mention of the occurrence of the sickle cells and phagocytosis of red blood cells by mononuclear cells in abnormal or anemic white subjects.

Bishop (1914) described the blood findings in an Englishman 41 years of age. In this subject about 75 per cent to 80 per cent of

the erythrocytes were elliptical in shape. The other blood findings in this case were essentially negative. The sister of this patient presented a similar blood picture. Huck and Bigelow (1923) reported two white cases presenting blood findings similar to those of Bishop's cases. Castana (1925) reported an infant of 15 months who showed a large number of "gigantocytes," the majority of which were half-moon shaped, and a few of which were sickle shaped and thread formed. He referred indiscriminately to two processes which are obviously not closely related. One of these was vacuolization of red blood cells, which has been described by Schilling-Torgau (1911) and Leede (1912). The second process was that of sickle cell anemia as described by Sydenstricker and others. Evidently he did not recognize the difference in the phenomena discussed by the above authors. His description leads one to believe that he has found true sickling phenomena, but his confusion of the two processes as stated above makes one accept this conclusion with some reservation. Furthermore, there is no specific statement that the case reported belongs to the white race, though the natural assumption is that the child was an Italian.

Cooley and Lee (1926) studied 400 colored patients for the presence of sickling phenomena and found sickle cells in 30, this number being seven and one half per cent of these cases. They stated that in regard to the children in their positive group "in general, there was nothing in the illnesses, symptomatology, physical findings, or clinical course to distinguish any of these 28 children from the ordinary negro patient, except the presence of sickle cells." They did not make any statement as to the usual number of sickle forms which they found in the cases reported. In no case did they find any phagocytosis of the red blood cells by mononuclear leucocytes. In regard to the degree of anemia in the two types of cases, they stated that "while moderate anemia seems to be the rule among our colored children, there is practically no difference in this regard between those with and those without sickle cells." Their findings of sickle cells represent a much higher percentage than previously reported.

The history of our first case described in this paper is difficult to evaluate. The patient remained in the hospital for such a short time that extensive observations could not be made. The neuro-

logical symptoms were thought, by a neurological consultant, to be evidence of posterior column degeneration but there was probably a definite hysterical element, also, as noted in the findings on physical examination. If there was cord degeneration, could this have been due to the type of anemia which the patient had? Certainly she did not have pernicious (Addison's) anemia, the usual form of anemia with which cord changes occur.

The blood findings were of particular interest and seem to have been those typically found in mild cases of sickle cell anemia, sickle- and sausage-shaped red blood cells, filamentation and phagocytosis being present. There must be some caution in calling this sickle cell anemia because no evidence of negro blood could be obtained. The familial tendency is of interest, one brother, one sister, and a niece presenting similar though less marked findings. Special attention was paid to the question of admixture of negro blood in the family and no evidence of this could be obtained. On the maternal side, the great-great-grandmother came from Spain and the great-great-grandfather from France. The great-grandparents came to Sumner County, Tennessee, and the family has remained there until the present. On the paternal side, the ancestry was Scotch-Irish, and the great-grandparents are thought to have settled in Virginia, the family later moving to Tennessee.

Approximately 3 per cent of the normal white adults and 5 per cent of 100 negroes (including both normal and sick individuals) in this series showed some deformity of the red blood cells, some of which seemed to be similar to those described in sickle cell anemia. Definite sickle forms were seen and, in addition, both long slender sausage forms and filamentous forms occurred. Questions naturally arise as to the etiological and clinical significance of these cells. Some of them were morphologically identical with those seen in sickle cell anemia, although these typical sickle cells were not present in as great numbers as were those of the slender sausage type, and we must raise the question as to whether these abnormal cells, occurring in apparently normal individuals or in patients suffering from some condition obviously unrelated to typical sickle cell anemia, have any relationship to the cells of true sickle cell anemia. There are several observations which indicate that these two types of cells have a similar if not wholly

identical etiology. First, in typical cases of sickle cell anemia, slender, elongated red blood cells are seen admixed with the typical sickle cells. Second, in most of the individuals in which the sausage cells were found, there were also typical sickle cells. Third, both types are characterized by the formation of slender filamentous processes which become free in the cytoplasm. Fourth, transitional forms have been seen between the two types. It seems possible, therefore, that the etiological factors involved in the production of these two types of cells are similar.

Various theories have been advanced as to the etiology of the true sickle cell forms, but no attention has been paid to the possible relationship between the different types referred to above. Emmel (1917) has advanced the hypothesis that the transformation of the red blood corpuscles into the sickle-shaped elements is due in part at least to an accentuated or abnormal activity of the same factors which in normal hematogenesis are involved in the transformation of the original spherical erythrocytes into biconcave disk-shaped forms. Sydenstricker, Mulherin and Houseal (1923) stated that "previous observers, in the absence of pathological examination of the cases and of any etiologic agent that could be discovered, have been inclined to ascribe the peculiar poikilocytosis present in this condition to changes that took place in the blood after the cells reached the peripheral circulation." These observers found cells in the marrow which they described as "sickle shaped, filiform and otherwise abnormal erythroblasts, with erythrocytes to correspond to those various types," and accordingly, they thought that these findings justified the conclusion that sickle cells seen in the peripheral blood were not the result of changes that went on in the circulation or in the splenic sinuses, but that these cells were performed in the marrow as the result of some primary fault of erythropoiesis. Huck (1923) has suggested the theory that the sickling of the red blood cells is due to something inherent within the cells and not to any substance in the serum. He further thought that it might be a surface tension phenomenon. Graham (1924) advanced the tentative working hypothesis in regard to sickle cell anemia that the condition might consist in an underlying status, determined primarily by deeply rooted racial characteristics and brought into clinical evidence in

occasional persons through the immediate action of toxic, metabolic or infectious exciting agents. He stated that there was some evidence in favor of the streptococcus being the immediate causative factor. Josephs (1927) has shown that the element responsible for sickling is in the plasma, since he has found that the abnormal erythrocytes of sickle cell anemia resume their normal shapes when washed sufficiently. Hahn and Gillespie (1927) have advanced evidence which indicates that "sickle cell formation in vivo is probably induced or increased by anoxemia." They think, however, that "the only specific cause for active sickle cell anemia is the unique hereditary anomaly of the red corpuscles which predisposes to it." However, the exact causative factor remains unknown.

Assuming that the factors which produce sickle and sausage cells are both identical or closely related, and since evidence that this process is present in an appreciable number of otherwise normal white adults has been obtained, it would seem that there may be an unknown factor at work even in the white race. But if this is true, apparently there is a definitely inhibitive force present also, for were this not the case, with this appreciable number of subjects having this unknown or α factor, many outstanding cases of sickle cell anemia in white subjects should occur. Are we to assume that these apparently normal white adults have quiescent sickle cell anemia? Do they really represent the earliest form of this condition, an intermediate form being represented by the white patient (L. B. S.)? It would seem possible that these individuals have a very mild form of the condition necessary for the production of sickle cell anemia. That they will ever develop the disease is doubtful. However, it may be that this α factor would become prominent were there to be an admixture of white and colored bloods, that is, the factor of sickling may become more prominent due to the interbreeding. This, of course, is highly speculative. It should be noted that only one case of sickling was found among the 42 apparently normal colored subjects examined. The other four cases found were among colored patients representing a variety of pathological conditions.

The picture presented in the two colored patients (W. P. and E. W.) is very similar to that reported in the normal white adults. The main differences are to be found in the presence of phagocytosis, the anemia

(1926) and Huck (1923), had found the fragility test particularly abnormal in sickle cell anemia, this test was not done

This opportunity is taken to express appreciation for the many helpful suggestions of Dr Robert S Cunningham, who has observed the blood in most of the cases reported in this paper

SUMMARY

1 Sickle-shaped, sausage and filamentous red blood cells have been shown to be present in some, otherwise normal, white adults

2 A corresponding series of negroes has shown these abnormal cells in approximately the same proportion (about 2 per cent)

3 A case presenting most of the blood findings generally associated with sickle cell anemia has been found in a white woman

4 The sickling phenomena have been found in certain members of her family

5 Evidence of sickling of red blood cells has been found in 6 white adults and in 4 colored adults suffering with various diseases

6 The cells of negro patients showed slight evidence of latent sickling and definite phagocytosis of red blood cells by polymorphonuclear neutrophiles

7 The sickle cells in one of the colored cases did not change their shape on being kept at incubator temperature

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THE EFFECT OF INSULIN, PITUITRIN AND ADRENALIN ON THE BLOOD-SUGAR LEVEL¹

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INTRODUCTION

In 1913, Stenström (1) showed that simultaneous injections of pituitrin and adrenalin prevented the development of hyperglycemia obtained from adrenalin injections alone. In 1923, Burn (2) confirmed this observation and also showed that injections of the posterior lobe of the pituitary gland inhibited the hypoglycemic action of insulin. Stenström concluded that there was an antagonism between adrenalin and pituitrin, and Burn, that there was an antagonism between insulin and extract of the posterior lobe of the pituitary gland. It thus appears that the secretion of the pituitary gland may have a dual action in the regulation of the blood sugar level, helping to prevent hyperglycemia on the one hand and hypoglycemia on the other.

In this paper are reported experiments which bear out Burn's conclusions in regard to the opposite effect on blood sugar of pituitary extract and insulin. They perhaps may help to explain the cause of the antagonism noted by Stenström and Burn between pituitary extract and adrenalin.

METHODS

The experiments were made upon normal rabbits. The samples of blood were obtained from the heart by means of a syringe and fine needle. Determinations of the level of the blood sugar concentration were made on 1 cc. blood samples according to the method of Folin and Wu (3), Lilly's Insulin, Parke, Davis and Co.'s Surgical Pituitrin and H. K. Mulford's Adrin (adrenalin solution 1:1000) were used.

¹ The expenses of this work were in part defrayed by the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

throughout Varying amounts of the drugs were injected in the marginal ear vein of the animals in the different experiments

RESULTS

The effect of insulin on the blood-sugar level

So many data have been already reported in regard to the effect of insulin upon the blood-sugar concentration that it is needless to give more than a summary of our own observations. Convulsions from hypoglycemia were prevented by light amytal anesthesia. This

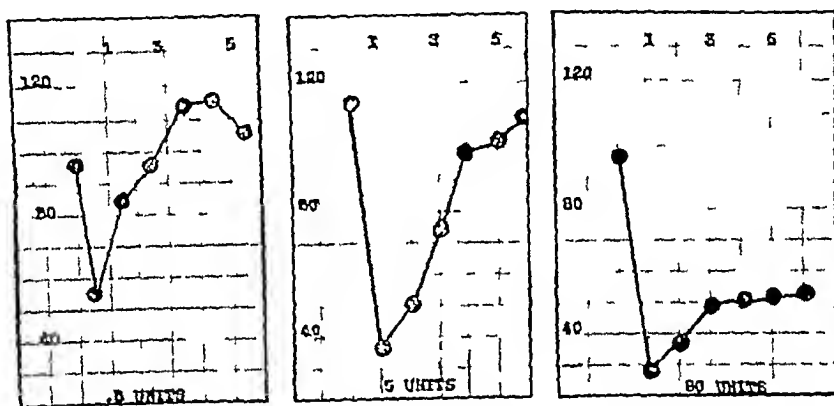


FIG 1 THE EFFECT OF VARYING DOSES OF INSULIN UPON BLOOD-SUGAR CONCENTRATION

The blood-sugar concentration is recorded in milligrams per 100 cc of blood, the time interval in hours

form of anesthesia was selected because, as first shown by Page (4), it has little or no influence on blood-sugar. The injection of insulin was invariably followed by a preliminary fall in the blood-sugar level and then by a secondary rise. This effect was obtained regardless of the amount injected. The chief difference in effect between a small dose and a large dose of insulin was that when large doses were given the resultant hypoglycemia lasted for a longer time than when small doses were employed. This fact is demonstrated by the blood-sugar curves from three typical experiments shown in figure 1.

The effect of pituitrin on the blood-sugar level

Burn showed that the injection of pituitary extract may be followed either by hyperglycemia or hypoglycemia. Our observations agree

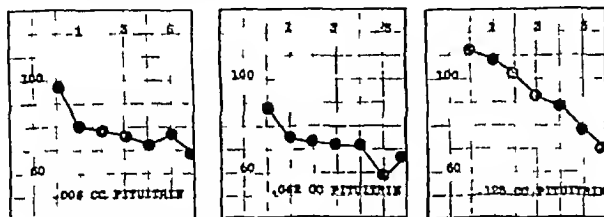


FIG II HYPOLYCEMIA PRODUCED BY VARYING DOSES OF PITUITRIN

The blood-sugar concentration is recorded in milligrams per 100 cc of blood, the time interval in hours

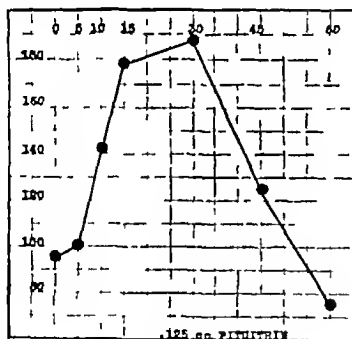


FIG III HYPERGLYCEMIA PRODUCED BY PITUITRIN

The blood-sugar concentration is recorded in milligrams per 100 cc. of blood, the time interval in minutes

with his. In certain of our pituitrin experiments the injection of the drug was followed by hyperglycemia and in others by hypoglycemia. Since we wish to emphasize particularly the production of hypo-

glycemia after pituitrin injections, three curves illustrating this action are inserted in figure II

In connection with these experiments, however, is one important feature which was perhaps not sufficiently stressed by Burn, but was emphasized by Stenstrom. The *immediate* effect of an intravenous injection of pituitrin, always, is to produce hyperglycemia. Such hyperglycemia may be transitory and may be overlooked unless blood samples are drawn at sufficiently frequent intervals after the drug is injected. In figure III is recorded a sugar curve to illustrate this point

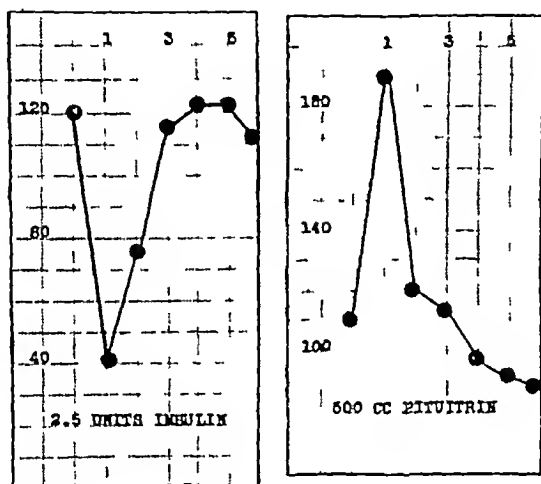


FIG IV A COMPARISON OF INSULIN AND PITUITRIN BLOOD-SUGAR CURVES

The blood-sugar concentration is recorded in milligrams per 100 cc of blood, the time interval in hours

In this experiment, had blood samples been drawn at hourly intervals instead of at more frequent intervals, the hyperglycemic effect of pituitrin would have been overlooked and the pituitrin injection would have been followed, seemingly, by a fall in the blood-sugar level

We were impressed, as was Burn, by the apparently opposite effect of insulin and pituitrin. The injection of insulin was followed by a sharp fall in the blood-sugar concentration and a subsequent rise to normal. The injection of pituitrin was followed by a sharp rise in the

blood sugar concentration and a subsequent fall to normal or below when properly graduated doses of the two drugs were given the resultant blood sugar curves were almost directly the opposite of one another. A comparison of typical insulin and pituitrin blood-sugar curves is shown in figure IV

The effect of adrenalin on the blood-sugar level

The effect of adrenalin upon blood-sugar concentration is as well known as that of insulin. The injection of adrenalin is followed by an

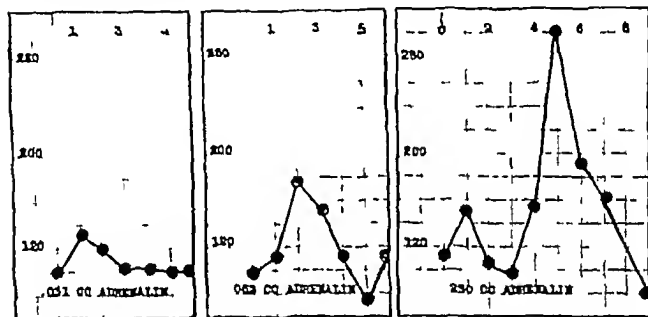


FIG. V. THE EFFECT OF VARYING DOSES OF ADRENALIN UPON BLOOD-SUGAR CONCENTRATION

The blood-sugar concentration is recorded in milligrams per 100 cc. of blood, the time interval in hours

increased blood-sugar concentration and then by a gradual return toward normal. In our experience, however, the blood sugar curves obtained with adrenalin were bizarre in contrast to those obtained with pituitrin, being less regular, and the curves being less strikingly the opposite to insulin than those obtained with pituitrin. Illustrative adrenalin curves are given in figure V.

Adrenalin hyperglycemia, too, as pointed out by Stenström, usually lasted for a longer period of time than the hyperglycemia obtained with pituitrin and disappeared more gradually. In this way adrenalin hyperglycemia resembled the hyperglycemia produced from the

intravenous injection of glucose and differed from that obtained with pituitrin. This difference between adrenalin and pituitrin hyperglycemia is shown in figure VI.

Does pituitrin mobilize insulin?

We wondered whether the relatively rapid fall in blood-sugar concentration so often observed after pituitrin injections could be due to the mobilization of insulin and to a different mechanism from

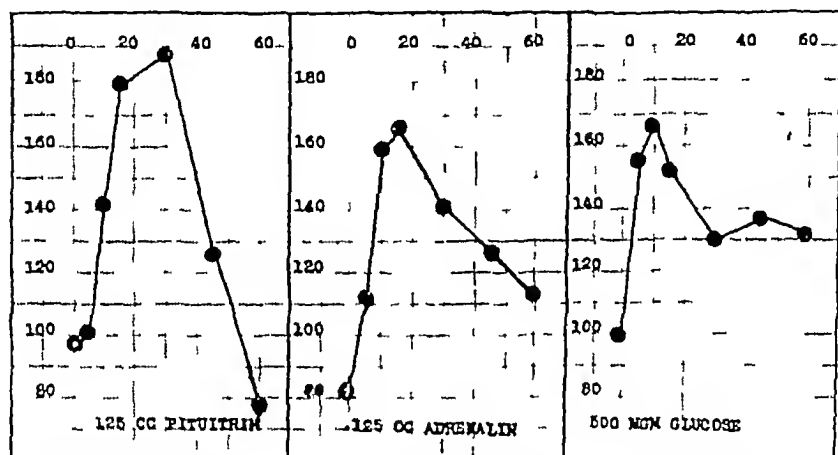


FIG VI A COMPARISON OF THE RATE OF DISAPPEARANCE OF HYPERGLYCEMIA PRODUCED BY PITUITRIN, ADRENALIN AND GLUCOSE

The blood-sugar concentration is recorded in milligrams per 100 cc of blood, the time interval in minutes

that producing the more gradual and less regular fall in blood-sugar level after the injection of adrenalin

We attempted to study this point by means of transfusion experiments. Twenty-five cubic centimeters of blood were removed from the heart of a normal animal, prevented from coagulating with sodium citrate, kept at body temperature in a water bath, and slowly injected into the ear vein of a second animal. Samples of blood from the recipient animal were withdrawn from the heart at intervals after the transfusion was completed and analyzed for sugar. It was possible to perform the transfusion on an animal under light amytal

anesthesia without difficulty and about twenty minutes' time was taken to complete the injection. The result on the blood-sugar level of such a transfusion of normal blood is illustrated in figure VII.

As can be seen, the transfusion was followed by a slight rise in the blood-sugar concentration with a gradual return to normal.

An animal was injected with five units of insulin and fifteen minutes later 25 cc. of blood was withdrawn from the heart, this blood being injected into a second animal. We estimated that under these condi-

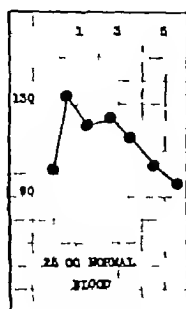


FIG VII

FIG VII THE EFFECT OF TRANSFUSED NORMAL BLOOD UPON BLOOD-SUGAR CONCENTRATION

The blood-sugar concentration is recorded in milligrams per 100 cc. of blood, the time interval in hours

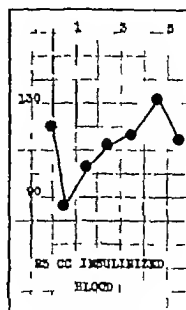


FIG VIII

FIG VIII THE EFFECT OF TRANSFUSED "INSULINIZED" BLOOD UPON BLOOD-SUGAR CONCENTRATION

The blood sugar concentration is recorded in milligrams per 100 cc. of blood, the time interval in hours

tions such an amount of the donor's blood would contain approximately one half a unit of insulin—a quantity of insulin sufficient, as already demonstrated, to have an appreciable effect upon the blood-sugar level of a normal animal. The result of this experiment is illustrated in figure VIII.

There was a slight fall in the blood-sugar concentration as a result

of this procedure followed by a gradual return to normal. The blood-sugar curve was like that obtained with a small dose of insulin and we are inclined to accept the finding as due to the insulin content of the transfused blood.

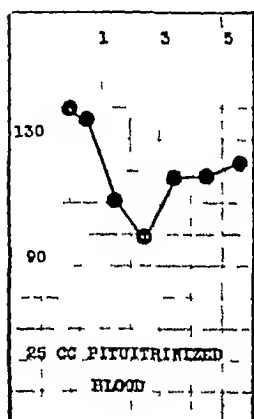


FIG IX

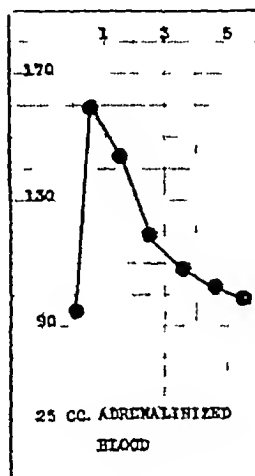


FIG X

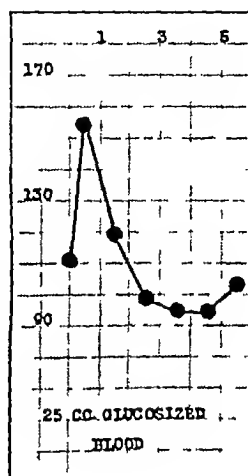


FIG XI

FIG IX THE EFFECT OF TRANSFUSED "PITUITRINIZED" BLOOD UPON BLOOD-SUGAR CONCENTRATION

The blood-sugar concentration is recorded in milligrams per 100 cc of blood, the time interval in hours

FIG X THE EFFECT OF TRANSFUSED "ADRENALINIZED" BLOOD UPON BLOOD-SUGAR CONCENTRATION

The blood-sugar concentration is recorded in milligrams per 100 cc of blood, the time interval in hours

FIG XI THE EFFECT OF TRANSFUSED "GLUCOSIZED" BLOOD UPON BLOOD-SUGAR CONCENTRATION

The blood-sugar concentration is recorded in milligrams per 100 cc of blood, the time interval in hours

An animal was injected with 0.250 cc of pituitrin solution and an hour and a half later 25 cc of blood was withdrawn from the heart, and injected into a second animal. This time interval was allowed to elapse after the pituitrin injection and before the bleeding so that

the blood would be obtained at a time when the blood sugar level was falling toward normal from the peak of the pituitrin hyperglycemia, and at a time when we believed that if the reaction were due to insulin, its presence might be demonstrated by this method. The donor's blood sugar level at the time of bleeding was 0.09 per cent. The result of this experiment is recorded in figure IX.

There was a slight fall in the blood sugar concentration after the transfusion, followed by a gradual return to normal. The resultant curve was much like that obtained from a small dose of insulin and in the transfusion experiment with "insulinized" blood.

An animal was injected with 0.500 cc of adrenalin solution and four hours later 25 cc of blood was withdrawn from the heart and injected into a second animal. This time interval was allowed to elapse before the bleeding so that the blood would be obtained at a time when the blood-sugar level was falling toward normal from the peak of the adrenalin hyperglycemia and when the presence of insulin might be demonstrable if the falling blood-sugar value were due to this substance. In this experiment the donor's blood sugar concentration at the time of bleeding was 0.10 per cent. The result of this experiment is recorded in figure X.

Here there was a slight rise in the blood sugar concentration after transfusion followed by a gradual return to normal. The resultant curve was like that obtained when normal blood was transfused and did not resemble that obtained with "insulinized" or "pituitrinized" blood.

Finally, an animal was injected with 750 mgm of glucose and an hour and a half later 25 cc of blood was withdrawn from the heart and injected into a second animal. This time interval was allowed to elapse before the bleeding so that the blood would be obtained at a time when the blood sugar level was falling toward normal from the peak of the hyperglycemia so induced and when the presence of insulin might be detected if the falling blood sugar value were due to this substance. In this experiment the donor's blood-sugar concentration at the time of bleeding was 0.10 per cent. The result of this experiment is recorded in figure XI.

There was a slight rise in the blood sugar concentration after transfusion followed by a gradual return to normal. The resultant curve

was like that obtained when normal or "adrenalinized" blood was transfused, and did not resemble that obtained with "insulinized" or "pituitrinized" blood

It is a question of how much importance can be attached to these transfusion experiments on account of their artificiality. Certainly, the inference from them is that under the conditions stated the "pituitrinized" blood contained an appreciable amount of insulin and that the "adrenalinized" blood did not. The hyperglycemia produced by pituitrin seemed to disappear rapidly as the result of mobilization of insulin, while the hyperglycemia produced by adrenalin disappeared gradually and without the assistance of an appreciable amount of insulin. The results with "adrenalinized" and "glucosized" blood are at variance with the experiments of Zunz and La Barre (5) who were also interested in the possible stimulation of insulin by hyperglycemia of various sorts. Zunz and La Barre made transfusion experiments in dogs by anastomosis of the pancreatic vein of the donor to the jugular vein of the recipient animal. When the blood-sugar level of the donor was raised by injection of sugar or adrenalin into the saphenous vein, the blood-sugar level of the recipient animal diminished, a finding which they interpreted as due to a compensatory hyperinsulinemia.

If it is true as our experiments suggest, that pituitrin hyperglycemia mobilizes insulin to a greater extent than does adrenalin, this may explain Stenstrom's observation that extract from the posterior lobe of the pituitary gland when given simultaneously with adrenalin inhibits the development of adrenalin hyperglycemia. For, if the injection of pituitrin increases the available insulin in a comparatively short space of time, one might expect the longer continued hyperglycemia induced by adrenalin to be offset by such an insulin effect of pituitrin. The prompt initial hyperglycemia produced by pituitrin probably explains why insulin reactions can be immediately prevented by this substance.

SUMMARY AND CONCLUSIONS

This paper reports experiments in normal rabbits in regard to the effect of intravenous injections of insulin, pituitrin and adrenalin on the blood-sugar level. Insulin caused a fall in blood-sugar concen-

tration followed by a rise to normal. Pituitrin and adrenalin caused a rise in blood sugar concentration followed by a fall to normal or below normal. The blood-sugar curves obtained with insulin and pituitrin were almost directly the reverse of one another. Blood sugar curves obtained with adrenalin were not so directly the reverse of those obtained with insulin and differed from those obtained with pituitrin in that the resultant hyperglycemia was of longer duration and subsided more gradually.

The rapid fall in blood-sugar concentration which developed following the injection of pituitrin appeared due to a recognizable increase in the circulating insulin, while the gradual fall in blood-sugar concentration which developed following the injection of adrenalin did not appear due to a significant increase in the circulating insulin. The basis for this conclusion lies in transfusion experiments. The injections of "insulinized" or "pituitrinized" blood in an animal was followed by slight hypoglycemia. The injection of normal blood, of "adrenalinized" blood or of blood made hyperglycemic by glucose in an animal was followed by slight hyperglycemia.

These experiments bear out the views of Burn in regard to the antagonism which exists between extract of the posterior lobe of the pituitary gland and insulin, and offer a possible explanation for the antagonism between pituitrin and adrenalin noted by Stenström.

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CHRONIC NEPHRITIS WITH AND WITHOUT EDEMA A STUDY OF CHOLESTEROL IN THESE CONDITIONS

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Many attempts have been made to correlate the clinical symptoms and pathological changes in the kidney of chronic nephritis, but so far, no general agreement prevails concerning the importance of numerous factors held partially accountable for some of the chief symptoms. This is well illustrated in the case of edema, where many theories have been advanced to explain its presence, and have not been generally accepted, as shown by the extensive review of Loeb (1).

Recently, considerable attention has been given to changes in the protein and lipid content of the blood plasma in renal diseases especially in cases of pure lipid nephrosis. Numerous studies have appeared dealing with protein changes and their relation to symptoms of nephritis, while comparatively few have dealt with cholesterol and its association with nephritis. This article takes up observations made on a series of cases of chronic nephritis with and without edema and includes a few cases of hypertensive cardiovascular disease with edema from heart failure. The changes in the blood cholesterol, the presence of cholesterol esters in the urine and in the tubular epithelium in those conditions are especially dealt with. To avoid confusion, it should be understood that no cases of pure lipid nephrosis are included here. The latter condition was studied and reported upon elsewhere (2).

Of the thirty-one cases reported here, twenty-five had chronic nephritis and six were cases of hypertensive cardiovascular disease with edema from heart failure. Of the twenty-five patients with chronic nephritis, fourteen were edematous, in eleven no edema appeared, seventeen died, and fourteen of these were examined post mortem. Three of the six patients with hypertensive cardiovascular disease died and were examined post mortem.

All of the patients classed as nephritis showed extensive glomerular involvement and the tubules were diseased in varying degree, from cloudy swelling to complete obliteration. Clinically, all the cases of nephritis under consideration fulfilled the requirements for a diagnosis of chronic diffuse glomerular nephritis. Under older classifications, those cases showing the edema, a heavy albuminuria, with slight retention of nitrogenous products would be classed as chronic parenchymatous, while those with no edema, an excessive retention of nitrogenous products in the blood, and a great elevation of the blood pressure, would be placed with the chronic interstitial type. Under the classification of Christian (3) many of these cases would correspond to his combined type, chronic nephritis with edema and hypertension, the others would conform to his group chronic nephritis with hypertension. Large and small white kidneys, mottled kidneys, and granular kidneys were found in this series. It seems significant that the edema appeared to be independent of either glomerular involvement or of simple tubular degeneration. The size, shape or color of the kidney bore no relation to the dropsy. Histologically, all cases exhibited tubular changes but those of the group showing edema were characterized by a special type of disease, namely, a lipoid deposit in the tubular epithelium, while those having no edema, had no lipoid deposit in the tubular epithelium.

The chief object of this paper is to show that there exists an association between chronic glomerular nephritis with edema on the one hand, and on the other, the following group of conditions: an elevation of the blood cholesterol, deposits of lipoid material in the tubular epithelium and the presence of doubly refracting lipoid bodies in the urine. As to the character of the association of the edema and the conditions mentioned—whether it points to a relationship as of cause and effect—even in the face of grave suspicion arising from a study of the cases, prudence suggests that judgment be suspended. For while these findings are present too constantly to be considered as mere coincidence, the significance of them in connection with the presence or absence of edema is obscure and may be related to other factors whose importance in this connection is still unknown.

COMMENT ON CASE HISTORIES AND AUTOPSY FINDINGS

(For detailed data see tables 1, 2 and 3, and appended protocols)

The cases presented may be divided into three groups Group I, patients with chronic nephritis with edema (table 1), Group II, patients with chronic nephritis with no edema (table 2), and Group III, patients with hypertensive cardiovascular disease with edema from heart failure (table 3) Besides the routine examinations, the blood cholesterol was determined and the urine examined for doubly refracting lipoids in each case, and where autopsies were performed the tissue was examined for doubly refracting lipoids

Cases in Group I (table 1)

There were fourteen cases in this group, nine of them died of uremia and five are living A post mortem examination was made in six The chief clinical findings were edema, hypertension, hematuria and a reduced renal function progressing to a serious degree of renal insufficiency and terminating in uremia Usually there was an elevation of blood cholesterol, although in case 12 it was subnormal and in case 2 it was only slightly elevated The edema was usually not persistent, but came and went at irregular intervals and was not influenced to a great extent by any treatment instituted Hypertension of varying degrees was present in all cases There was some elevation of blood urea nitrogen in all cases, although in case 10, the increase was not great Doubly refracting lipoids were found almost constantly in the urinary sediment of all cases except in case 12 where none was found on repeated examination These lipoids were found regularly in all the cases during edema free period It can be said that the magnitude of the edema was not matched by the number of doubly refracting lipoids present in the urine It may also be stated that the degree of hypercholesterolemia did not parallel the amount of edema at all times There was an extensive edema in case 6 at a time when the blood cholesterol was less than usual Of the kidneys of this group examined post mortem, all had doubly refracting lipoids in the renal tubular epithelium, including case 12, in which none was found in the urine during ante mortem observation The lipoids were found in the convoluted and straight tubules as a rule, and at

TABLE 1
Detailed data of cases in Group I (chronic nephritis with edema)

Case number	Age	Date	Blood					Function tests		Edema	Urine			Remarks
			Blood pressure		Urea nitrogen	Cholesterol	Creatinin	Phthalain per cent per 2 hours	Urea concentration factor		Albu min	Doubly refracting lipoids	Microscopic	
			Systolic	Diastolic										
1	50	June 2 1926 June 16, 1926 June 21 1926 June 24 1926 June 29, 1926 July 2 1926	180/110 205/125 195/115 180/120 230/125 188/110	56 63 57 78 78 44	9.375 9.295 57 210 78 44	0 0 0 0 0 0	5 10 10 10 10 12	15 10 10 10 10 10	8 4 	Extensive Extensive Decreased Decreased Increased Extensive Extensive Extensive Extensive Marked Marked Slight Gone Gone Gone Excessive Excessive Excessive	++++ ++++			

6	23	October 4 1926 November 1 1926 January 4 1927 February 15 1927	170 103 23 0 397 0 160 98 408 0 160 110 26 2 350 0 160 100 33 0 350 0	60 50 45 0 35		Moderate Slight Slight Excessive	++++ ++++ ++++ ++++	Present Present Present Present	Red blood cells, pus cells, granular casts	Improving
7	39	July 1 1925 July 18, 1925 July 22, 1925	175 100 46 0 365 0 205 150 65 0 210 140 74 0	2 2 3 2 0	8 4	Extensive Extensive Extensive	++++ ++++ ++++	Many Many Many	Red blood cells pus cells, granular casts	Died in uremic coma July 23 1925
8	13	November 7 1925 December 22 1925 January 13 1926 April 28 1926 May 15 1926 June 25 1926 November 21 1926 December 5 1926 January 27 1927	118 60 14 9 120 75 14 3 125 60 27 0 510 0 120 70 9 8 420 0 115 75 14 4 468 0 125 65 8 2 416 0 144 65 35 6 250 0 135 80 24 0 260 0 145 90 304 0	1 5 55 65 60 1 0 45 65 55 55 304 0	70 0 68 0 65 0	Moderate Less Present Slight Of face Slight Moderate Present	++ ++ ++ ++ ++ ++ ++++ ++++ ++++	Present Present Present Present Present Present Present Present	Many red blood cells pus cells, granular casts Few red blood cells, pus cells, granular casts Many red blood cells, pus cells and casts	Going to school every day
9	42	September 2 1923 December 4 1925 December 25 1925 February 1 1926	210 140 26 0 185 100 18 2 185 110 14 9 185 110	2 2 35 45 1 6 40 375 0	42 0	Mild Extensive Extensive Extensive	+++ ++++ ++++ ++++	Not looked for Not looked for Not looked for Many pres- ent	Few red blood cells and pus cells, granular casts Granular casts, few red blood cells and pus cells	Died in uremic coma Feb- ruary 19 1926
10	29	January 20 1927 January 30 1927 February 6, 1927	145 95 23 0 324 0 134 60 15 4 362 0 124 70 18 2	60 50 50 0	54 0 50 0	Slight Gone Gone	++++ ++++ ++++	Many Many Many	Many granular casts, pus cells, red blood cells	Complained only of edema Feeling better Discharged
11	22	September 11 1925 October 13 1925 November 15 1925	185 120 40 5 420 0 175 110 180 120 21 0	2 9 20 25 21 0	35 0	Extensive Extensive Extensive	++++ ++++ ++++	Many pres- ent	Few red blood cells, granu- lar casts, pus cells Few pus cells, few red blood cells and granular casts	Worse Died in uremic coma November 20 1925

TABLE 1—Continued

Case number	Age	Date	Blood					Function tests		Urine			Remarks
			Blood pressure		Urea nitrogen	Cholesterol	Creatinin	Phthalatein per cent per 2 hours	Urea concentration factor	Albumin	Doubly refracting lipoids	Microscopic	
			Systolic	Diastolic									
12	55	December 23, 1926	230	130	51.4	104.0	4.2	10	15.0	+++	None	Pus cells, no casts	Died in uremic coma January 18, 1927
		December 30, 1926	240	150	47.0	109.0		10		+++	None	Many pus cells, red blood cells and granular casts	
		January 12, 1927	220	138	80.3	103.0	5.1	10	0	+++	None		
13	40	October 27, 1924	220	118	25.0			60		+++	Not looked for	Granular casts, red blood cells, pus cells	Improved Died in uremic coma October 20, 1925
		February 12, 1925	210	140	28.0			50		+++	Not looked for		
		June 7, 1925	200	110	40.0	333.0	1.0	35	2.0	+++	Present		
		August 8, 1925	190	120	16.0	294.0		45	1.75	+++	Present	Granular casts	
		October 17 1925	205	125	42.0	316.0		10		+++	Present		
14	30	October 6 1926	220	110						+++			Died in uremic coma January 30, 1927
		December 29, 1926	240	120				6		+++	Present	Pus cells, red blood cells, granular casts	
		January 20, 1927	220	130	67.0	390.0	3.8			+++	Many		

times in the interstitial tissue. Tissues were stained for fat and it should be emphasized that not all the fat was doubly refracting but that there was a mixture of fats present.

At times, cases similar to those in this group are called by some, pure lipid nephrosis because of the presence of edema, hypercholesterolemia and doubly refracting lipoids. Confusion may arise between pure lipid nephrosis and chronic glomerular nephritis with secondary lipid degeneration in conditions as in case 10. Case 10 showed edema, hypercholesterolemia, doubly refracting lipoids in the urine and albuminuria, findings common to both conditions. The elevation of the blood pressure and the presence of red blood cells and granular casts in the urine served to make a diagnosis of glomerular nephritis. When patients have a quiescent chronic glomerular nephritis, with albuminuria and very few cellular elements, the history of having had indications of glomerular nephritis previously may help in the differential diagnosis. The hypercholesterolemia usually is greater in pure lipid nephrosis than in chronic glomerular nephritis with secondary lipid degeneration of the tubules. Histological examination of renal tissue from patients with pure lipid nephrosis shows the glomeruli to be practically normal and that from patients with chronic glomerular nephritis with secondary lipid degeneration of the tubules reveals well defined glomerular lesions. The distribution of lipid deposits is quite uniform in the former condition, while in the latter there is a selective arrangement of the deposits. Dewey (4) observed a selective localization of lipoids in the renal tubules in animals injected with cholesterol. In all the cases of Group I (with edema), where post mortem examination of the kidney was made, the tubules showed deposits of doubly refracting lipoids. There was a mixture of cholesterol esters and other fats. The association appears to be closer between edema and deposits of lipoids in the tubules than between the hypercholesterolemia and edema, or the lipoids in the sediment and edema.

Cases in Group II (table 2)

There were eleven cases in this group, and of them ten died and were examined post mortem. Clinically the cardinal signs and symptoms of chronic glomerular nephritis were present, but in contrast to

TABLE 2
Detailed data of cases in Group II (*chronic nephritis without edema*)

Case number	Age	Date	Blood				Function tests		Edema	Urine			Remarks	
			Blood pres sure	Urea nitrogen		Cholesterol	Creatinin	Phthalatein per cent per 2 hours		Urea concentration factor	Albumin	Doubly refracting lipoids		Microscopic
				Systolic	Diastolic									
15	58	February 5, 1927 February 7, 1927	180 165	112 100	65 94	0 0	172 111	0	Absent Absent	+++ +++	None None	Many pus cells, granular casts and red blood cells	Died in uremic coma February 7, 1927	
16	31	October 17 1926 October 20, 1926 October 24, 1926	250 210 125	150 140 95	67 82 40	0 0 0	205 190 175	3 0 0	Absent Absent Absent	+++ +++ +++	None None None	Many red blood cells, pus cells and granular casts	Died of pericarditis and uremic coma October 25, 1926	
17	52	December 2, 1926 December 7 1926 December 17, 1926 December 21, 1926	188 195 180 190	126 125 110 130	47 69 84 81	6 3 0 0	156 172 186 130	2 6 0 7	15 10 6 5	Absent Absent Absent Absent	+++ +++ +++ +++	None None None None	Granular casts, pus cells, red blood cells Increased in amount	Worse Died in uremic coma December 25 1926
18	25	October 23, 1926 November 27, 1926	190 196	116 100	37 24	2 2	255 205	0 0	23 25	Absent Absent	++ ++	None None	Many granular casts, red blood cells and pus cells	Living and well
19	50	February 1 1927 March 3, 1926 April 15 1926 July 13, 1926 September 24, 1926 October 15, 1926	172 240 205 230 184 190	120 130 120 140 122 118	18 24 14 31 122 61	0 4 8 8 74 0	154 160 152 185 0 0	1 0 2 0 3 2	10 9 15 2 8 5	Absent Excessive Decreased Excessive Marked Excessive	+++ +++ +++ +++ +++ +++	None None None None None None	Very few red blood cells and pus cells granular casts Many granular casts	Edema due to heart failure Died of pneumonia October 16, 1926

20	42	October 26 1924	240 150	84 0 203 0	2 3 7		Absent	++ ++	None	Many granular casts, red blood cells and pus cells	Died in uremic coma January 11 1925
		November 7 1924	193 140	92 0		5	Absent	++ ++			
		December 18, 1924	218 160	120 0 175 0	5 7 5		Absent	++ ++			
		January 9 1925	222 155			0	Absent	++ ++			
21	52	July 29 1925	290 125	32 2 154 0		15 60 0	Absent	++	None	Few red blood cells, pus cells and casts	Headache Had severe headaches
		August 20 1926	215 110	28 9		25	Absent	++	None		
	4	September 9 1926	205 100	36 0 147 0		42 0		+	None		
		October 20 1926	180 110	28 2 210 0				+	None		
		November 16 1926		42 8 160 0		15 45 0			None		
		December 13 1926	210 105	46 6 154 0		15			None		Died of apoplexy December 16 1926
22	36	February 24 1925	185 100	150 0 136 6	4 0	6	Absent	++ ++	None	Granular casts, red blood cells and white blood cells	Died in uremic coma February 28, 1925
		February 27 1925	193 120			0	Absent	++ ++			
23	32	November 12, 1925	240 150	34 5		15	Absent	++ ++	None	Red blood cells, pus cells and granular casts	
		December 18 1925	220 135	42 4	5 3 10		Absent	++ ++	None		
		February 23 1926	210 130	24 7		10 13 0	Absent	++ ++	None		
		May 5 1926	225 140	40 0 195 0 11 2		20	Absent	++ ++	None		
		September 15 1926	200 120	152 0 227 0 14 8	3 9 0		Absent	++ ++	None		
		September 18, 1926	190 70	105 0		0	Absent	++ ++	None		Died September 18 1926
24	47	January 30 1927	222 126	79 0 196 0			Absent	++ ++	None	Pus cells, granular casts and red blood cells	
		February 2, 1927	195 135	113 0 178 5 9 4			Absent	++ ++	None	Few pus cells and red blood cells	Died in uremic coma February 2, 1927
25	40	January 29 1927	270 136	59 0 156 0			Absent	++ ++	None	Pus cells, red blood cells, granular casts	Died in uremic coma February 4, 1927
		February 1 1927	215 124	63 0	4 1		Absent	++ ++	None		

* Rest.

† Respiration.

Group I, edema was absent. The blood cholesterol at times was elevated although usually it was normal or subnormal. No doubly refracting lipoids were found in the urinary sediments. These patients were for the most part older than those of Group I. Uremia terminated the course of the disease in eight cases and a plastic pericarditis was associated with uremia in three of them. In case 19, edema was present that had the features of a cardiac edema, findings also were present pointing to renal disease, the post mortem and clinical data indicated that the kidneys were severely damaged and for that reason the case is included in this group. All other cases in this group were free from edema. Practically all of the patients had unmistakable signs and symptoms of chronic diffuse glomerular nephritis. Cases 17 and 19 were diagnosed malignant hypertension (renal type) because of the extensive involvement of the arterioles and a history that pointed to a long standing hypertension. The lipid deposits seemed not to be influenced by the fact that the disease began in the arterioles of the kidney or in the glomeruli proper. Histologically, well developed chronic glomerular nephritis was found in all cases examined. The tubular epithelial cells were usually found to be extensively diseased but no doubly refracting lipoids were found in them. In cases 15, 20 and 24, fatty material was found with fat stains in the tubular cells, but none of this fat was doubly refracting.

Cases in Group III (table 3)

Of the six cases in this group, two died of heart failure and one of pulmonary embolism. The three were examined post mortem. These cases are included to demonstrate that the presence of edema in this type of disease is not associated, as a rule, with doubly refracting lipoids in the urine or in the renal tubules. Clinically, edema, chronic hypertension, and cardiac hypertrophy were the chief features. No doubly refracting lipoids were found in the urine except in case 29, where a few were found occasionally in the urinary sediment. The blood chemical data and renal function tests revealed less kidney involvement than in the first and second groups. There was no hypercholesterolemia. By comparing the results of polariscopic examination of the urine and renal tissues of this group with Group I, it is seen that here doubly refracting lipoids were practically always

Case number	Age	Date	Blood					Function tests		Edema	Urine			Remarks
			Blood pressure		Urea nitrogen	Cholesterol	Creatinin	Phthalein per cent per 2 hours	Urea concentration factor		Albumin	Doubly refracting lipoids	Microscopic	
			Systolic	Diastolic										
26	51	October 2 1925 August 15 1926 February 7 1927	215/124 205/118 195/110	16 0 21 2 14 8	16 0 240 0 164 0	2 4 30 1 2	55 30 55	59 0 46 0 29 0	Slight Extensive Moderate	+	None None Trace	Few pus cells Few granular casts, pus cells Hyaline casts Few pus cells, red blood cells Few granular casts	Well developed. Heart failure present. Improving Auricular fibrillation present. Died September 5 1926	
27	54	July 11 1926 August 15 1926 September 2 1926	242/130 235/140 186/112	10 7 17 0 15 0	185 0 172 0 165 0	1 4 1 6 2 5	25 20 25	46 0 2 1 29 0	Moderate Increased Extensive	+	None None None	Pus cells and red blood cells Granular casts Hyaline casts, many pus cells Few red blood cells, granular casts	Living and improving slowly	
28	48	February 15 1926 December 6, 1926 May 4 1926 June 1 1926	210/106 184/120 186/102 205 90	22 6 27 5 51 6 37 0	161 0 225 0 179 0 210 0	2 9 2 0 2 1 2 5	40 45 22 55	54 0 40 0 37 0 25 0	Moderate Extensive Extensive Moderate	++ ++ +++ +	None None None Few occasionally present	Pus cells and red blood cells Granular casts Hyaline casts, many pus cells Few red blood cells, granular casts	Improved	
30	46	November 2 1926 January 8, 1927 March 5 1927 May 17 1927	190 95 218/100 185/110 212/125	28 0 29 1 38 2 12 6	189 2 178 0 2165 0 6136 0	1 8 1 0 1 7 1 8	20 55 30 35	25 0 58 0 55 0 35 0	Decreased Extensive Extensive Extensive	++ Trace + ++	None None None None	Few red blood cells and pus cells None None None	Died of pulmonary embolism May 19 1927	
51	44	November 7 1926 February 17 1927 March 1 1927	196/115 210/105 186/110	25 0 15 7 37 0	208 0 175 0 37 0	2 5 2 4 3 2	25 30 20	44 0	Extensive Moderate Extensive	++ ++ +++	None None None	Few granular and hyaline casts Many pus cells and red blood cells	Died of cardiac failure March 3 1927	

absent (except case 29), while they were constantly present in Group I. At post mortem examination, the chief changes in the kidneys were lesions involving the smallest arterioles and an interstitial fibrosis. The glomeruli were also diseased but not so uniformly nor so extensively as in Groups I and II. Some glomeruli were found hyalinized and there was a moderate amount of capsular fibrosis. Many glomeruli were enlarged and others appeared normal. The tubular epithelial cells were found to be considerably less involved than those in the other groups. The diagnosis of this group depended more upon the clinical history, the renal function tests and the blood chemistry than on the histological examination. Usually these patients gave a history of having had hypertension with little or no albuminuria for years. In case 31, fatty material was found, but none of it was doubly refracting. None of the other kidneys of the group examined showed fat of any kind in the renal parenchyma.

THE POLARIZING MICROSCOPE

The use of the polarizing microscope in the differentiation of certain fatty substances was introduced in 1858 by a German physician, Mettenheimer (5). He called attention to the anisotropic nature of certain fatty substances then called myelins. Mettenheimer published his observations in an obscure medical publication that soon passed out of existence, and along with it went Mettenheimer's observations. The work of Kaiserling and Orgler (6) brought about renewed interest in the doubly refracting phenomenon of certain fats and since that time, the polaromicroscope has been in common use in Germany. Adam (7) in 1906 emphasized the importance of this instrument in studying pathological fatty changes. At that time Adam felt that it was very useful in pathology, and that its value was underrated. Although the polarizing microscope was utilized to advantage by a few investigators in Europe, the use of it has not been widespread especially in America and England. Boyd (8) recently contended that the polaromicroscope has not received the recognition that it merits in biological work. He believes it is absolutely essential in researches upon lipoids, and that it is remarkable that it has not come into more general use. Although other methods of differentiating cholesterol esters from other fats are used, the doubly

refracting phenomenon probably will always occupy an important place in such work, because of the simplicity of its recognition with the polarizing microscope. For the past two years, in connection with the work presented here, the polaromicroscope has been used routinely in examining kidney tissue removed or at autopsy. Urinary sediment, from all patients with any form of renal disease or heart disease, was examined routinely by this method. Despite the fact that the exact status of lipoids in Bright's Disease is not completely established, enough has been learned to insure them a place in clinical and research work of the future. Contrary to the general conception about it, the polaromicroscope is a simple device, and it seems that it is very useful in the clinical study of nephritis. In view of the fact that many particles in urinary sediment and in tissues are seen to shine brightly with the polariscope, it is better in diagnosis to rely upon the presence of the maltese crosses rather than upon the findings of particles with peculiar shades of brightness.

DISCUSSION

Why some cases of chronic glomerular nephritis have edema and others do not is an unsolved problem at present. Tubular degeneration is a part of the picture in all cases of diffuse glomerular nephritis. It is fair to assume that the glomeruli have been involved in so many cases of nephritis without edema, that they cannot be considered as the chief element in the cause of the edema. This would seem to be true, likewise, with the tubules, whose extensive involvement at times is not associated with edema. Opinions at present vary concerning the significance of chloride retention, plasma protein reduction and changes in the hydrophilic forces of the body colloids. Cholesterol, too, has been studied in a measure, clinically and experimentally, to determine its place in relation to the edema of nephritis. Port (9) was among the first to report a hypercholesterolemia in some case of chronic nephritis with edema. At about the same time Chauffard, Laroche and Grigaut (10) compared the cholesterol content of the blood in cases of cardiac and renal edema, and found an excess of cholesterol in blood of patients with nephritis and edema, while a normal amount was found in those with cardiac edema. They also stated that they studied six patients with chronic nephritis but edema

free, whose nitrogen in the blood was greatly elevated and the cholesterol content of blood was normal or only slightly raised. In those patients where edema was most extensive, the cholesterol of the blood varied from 285 to 800 milligrams per 100 cc. They concluded that the patients who had the greatest nitrogen retention had the lowest cholesterol content in the blood. In addition to the observations on the quantities of blood cholesterol in nephritics, Kaiserling and Orgler, (6) drew attention to doubly refracting lipoids in kidneys of patients with amyloid disease. Later, Adam and Aschoff (11) proved that the doubly refracting globules, previously called myelin by Virchow (12) were, in fact, cholesterol esters. Munk (13) while studying the influence of anisotropic lipoids in kidney diseases, pointed out the importance of finding them in the urinary sediment. He believed the presence of lipoids indicated a poor prognosis. More recently Munk (14) studied the significance of lipoid in filtration and tubular degeneration. The hypercholesterolemia, in his opinion, is any expression of abnormal metabolism, and the tubular cell changes are secondary to constitutional alterations and changes in the blood itself. It is his belief that the kidneys are injured during the process of excretion of cholesterol subsequent to a hypercholesterolemia.

Epstein (15) states that the hypercholesterolemia is a change dependent upon a metabolic disorder of thyroid origin. He does not take up the question of lipoids in urinary sediment and in the tubular epithelium.

That cholesterol by itself in excessive quantities may be sufficient to injure and destroy tubular epithelium was shown by Dewey (4), who injected cholesterol intravenously into rabbits and caused lipoids to be deposited in the epithelial cells of the tubules.

On the relationship of nephritis to cholesterol metabolism Kollert and Finger (16) found that a hypercholesterolemia was not indicative of a defective excretory power of the kidney, because in cases where a reduction in kidney was present, a hypercholesterolemia did not follow. They suggested that the increase in the blood cholesterol is due to a change in the function of the liver which is secreting bile low in cholesterol content. In relation to edema, these authors believe that with the excretion of cholesterol by the kidney, the edema disappears and that the edema returns when the lipoids again are not ex-

creted Stepp (17) considering the hypercholesterolemia in cases of Bright's disease, suggested that in the nephritic conditions the cholesterol originates from fatty degeneration of the kidney, but he could not substantiate this opinion Stepp carried out a study on the relation of blood cholesterol to different forms of Bright's disease He made no report of polaromicroscopic examination of the urinary sediment or of the kidney tissues Out of his 47 cases of acute and chronic Bright's disease, twelve died, and seven were examined post mortem. Those that showed a hypercholesterolemia had large smooth kidneys, with excessive disease of the tubular epithelium and marked edema Kahn (18) found that the cholesterol was not invariably increased in parenchymatous nephritis although it was increased at times in chronic interstitial nephritis

It was the opinion of Henes (19) that the quantity of blood cholesterol could be used as a prognostic index, that a hypercholesterolemia was found in cases when the outlook was favorable, and a low cholesterol content when the prognosis was less favorable

In a study of the lipoids in renal diseases, Daniels (20) found that the cholesterol of the blood was elevated in five out of seven cases of so-called chronic parenchymatous nephritis Eleven other cases of various diseases of the kidney manifested no increase in blood cholesterol He made no report of the presence or absence of urinary lipoids, but mentioned two cases in which lipoids were found in the tubules of sections removed from the kidney at time of decapsulation Interesting also, was his observation that in only one case was there a decrease in blood cholesterol, when the urea nitrogen became elevated Under the term "myelin kidney" M'Nee (21) described three cases, all of which showed glomerular nephritis with deposits of doubly refracting lipoids in the kidney tissues Edema was noted in two cases but not mentioned in the other He found that most of the lipid substance was deposited in the interstitial tissue of the cortex A smaller quantity was found in the epithelial cells of the convoluted tubules

In a recent article, Lowenthal (22) considered clinically and experimentally the connection between blood cholesterol, blood proteins, and water balance It seemed to him that the retention of lipoids paralleled the formation of edema and that the excretion of lipoids

paralleled the excretion of water. With the retention of water and the hypercholesterolemia, a decrease in the serum proteins was found. Lowenthal, by feeding animals cholesterol, was able to produce a hypercholesterolemia with histological changes in the kidney tubules similar to those found in lipoid nephrosis in humans. He did not investigate whether or not a true hydremia was induced, although he says that he did not cause edema. He concludes that a hypercholesterolemia is caused by a primary change in lipoid metabolism and that there is consequently a deposit of lipoids in the renal tubular epithelium. He pointed out that the relationship between salt, protein, cholesterol and water balance has to be worked out as a future problem.

These findings were in conformity with those of Heilig and Lederer (23) who found a relative and absolute increase in the blood cholesterol in cases of nephritic edema, and that the degree of edema paralleled the height of the blood cholesterol. After a study of one hundred cases of nephritis, Bing and Heckscher (24) reported that the edema was associated with an elevation of the blood lipoids. They furthermore claimed that an increase of the fat in food leads to an increase in lipemia with a consequent increase of the edema.

In connection with this association of lipoid degeneration of the tubular epithelium, hypercholesterolemia and edema, Fahr (25) concludes that the kidney is not primarily at fault. For the development of edema, he believes certain alterations of the capillaries of the skin are necessary, that on the other hand the formation of an edema in nephritic cases shows a quite definite relationship to the increased deposits of cholesterol, and furthermore the reticulo-endothelial apparatus, and also that of the subcutaneous tissues, participates in cholesterol metabolism. Hence the conclusion that hypercholesterolemia and the cholesterol infiltration of the kidneys are expressions of those disturbances which produce alterations in the capillary walls of the skin and of the subcutaneous tissue and that edema occurs only after these alterations. While he holds that the glomerular change is always present, but that this is not sufficient in itself to produce the extensive edemas found, he points out that the tubules themselves are not solely responsible, since extensive tubular degeneration may occur without manifestations of edema and therefore he thinks that some extra-renal factor must be present.

Cholesterol esters have been found deposited in the epithelial cells of the renal tubules by Weltmann and Biach (26) after they had fed a rabbit one gram doses of cholesterol daily for twenty-five days. Uranium nitrate was injected intra-peritoneally during the last seven days of the experiment. Control experiments without feeding cholesterol, but with injections of uranium nitrate, resulted in no lipid deposits.

Chalatow (27) has shown that cholesterol esters are deposited in cells which have been injured, especially when acid products are formed in cells, and this causes the cholesterol esters to be deposited. He also found that a hypercholesterolemia could be produced in animals but that this in itself was not followed by cell infiltration. When the cells were poisoned, a very slight rise in cholesterol in the blood caused deposits of cholesterol ester in the injured cells.

A study of the association of glomerulo tubular nephritis and nephrosis with edema was reported by Linder, Lundsgaard and Van Slyke (28). They dealt especially with the protein content of the plasma and its bearing on edema. It was concluded that there is no direct relationship of cause and effect between low protein concentration in the plasma and the presence and degree of edema. Furthermore, they pointed out that while fatty degeneration of the tubules is a conspicuous feature of the histological picture in nephrosis, and in nephrotic type of glomerular nephritis, it was found also in the tubules of those cases where little edema was found. They do not state, however, whether or not they differentiated between the doubly refracting lipoids and neutral fats. It would seem that had the urine been examined for doubly refracting lipoids in their cases of glomerular nephritis with nephrosis many would have been found.

In an article dealing with the pathology of nephritis associated with edema, Dyke (29) reported six cases of the type called by him chronic parenchymatous nephritis. Clinically, all were characterized by edema, histologically, by the presence of doubly refracting fat in the tubular epithelium. The glomeruli were impaired in all of the cases, in some only a degenerative change with deposition of fat was seen, in some inflammatory signs were present and in others an amyloid degeneration was found. He called attention to the fact that it was not the degeneration of the tubular epithelium itself but the occurrence of lipid deposits in them, that was of importance.

The subject of relationship between lipid degeneration of the tubules, hypercholesterolemia and edema is treated in an article by Bennet, Davies, and Dodds (30) They found that cases of renal edema, without hypercholesterolemia are conspicuously absent and they doubt whether such a condition occurs unless the edema is secondary to a failing heart Among the unsolved problems, these authors included the significance of hypercholesterolemia to the edema in lipid nephrosis, questioning whether it appears at the onset or follows a prolonged course of albuminuria

It has been assumed usually, that the edemas of nephritis and nephrosis differ both in composition and pathogenesis Epstein (31) has shown that the edema fluid of nephrosis is low in protein, while that of glomerular nephritis has a high protein content He attributes the edema of glomerular nephritis to an increase of capillary pressure with increased filtration The edema of nephrosis, he believes, is caused by a loss of plasma protein which is followed by an upsetting of the osmotic equilibrium between the blood and tissues which results in retention of water in the tissues

It has been questioned whether the combination of chronic glomerular nephritis with secondary lipid degeneration of the tubules in these cases constitutes an accidental association of two different diseases, or whether one is the result of the other It has been emphasized by Elwyn (32) that the frequency of the occurrence of the combination of the two conditions seems too uniform to be accounted for by mere coincidence The question that remains is why do some cases of glomerular nephritis remain free from lipid changes and others exhibit them? While it is seen that attempts have been made to show parallelism between hypercholesterolemia and edema, the results have not been conclusive Observations in this series of cases indicate that edema comes and goes irrespective of the height of blood cholesterol

In the discussion of cases it is seen that patients may have a hypercholesterolemia with no edema and no doubly refracting lipoids in the urine Chronic nephritic edema has been found to be invariably associated with a deposition of doubly refracting lipoids in renal tubules That the co-existence of these symptoms and the deposition of cholesterol esters in the tubular epithelium is mere coincidence,

seems untenable because of the constancy of their relationship in cases of chronic nephritis with and without edema

One is led to conclude that it is neither the elevation of cholesterol in the blood alone nor the disease of the tubular epithelium alone, that exerts an influence upon the mechanism of edema production, but that the combination of diseased tubular cells and the presence in these cells of cholesterol esters, is the factor which seems to be connected with edema formation

The histo-chemical analysis of the fatty substances of anisotropic character which I have mentioned and but briefly discussed has been omitted from this paper and is reserved for future detailed investigation This clinical study is being continued and experimental investigation is being made of the problems here suggested

SUMMARY

1 Thirty-one cases have been abstracted and discussed, fourteen had chronic glomerular nephritis with edema, eleven had chronic glomerular nephritis without edema, while six were cases of hypertensive cardiovascular disease with edema from cardiac failure The cases are classed into three groups and the characteristic features of each group are discussed

2 Emphasis has been laid on the fact that the presence of doubly refracting lipoids found in renal tubular epithelium and in the urinary sediment is associated with chronic nephritis and edema

3 It was pointed out that doubly refracting lipoids were rarely found in the urinary sediment of patients with hypertensive cardiovascular disease with edema from cardiac failure (Group III)

4 None of the patients having nephritis without edema had doubly refracting lipoids in the urine and in none were they found in the tubular epithelium at autopsy

5 A hypercholesterolemia was usually found in the cases of chronic nephritis with edema (Group I), while those cases of chronic nephritis without edema (Group II) and of hypertensive cardiovascular disease (Group III) usually had a normal cholesterolemia

6 A chronic diffuse glomerular nephritis was present in all the cases of chronic nephritis described

7 A review of some of the work done both clinically and experimentally upon the subject of cholesterol and nephritis is given

8 No theories have been advanced to explain these clinical observations as the clinical study is being continued and an experimental investigation is being made

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ABSTRACTS OF CASES HISTORIES AND AUTOPSY FINDINGS

GROUP I PATIENTS WITH CHRONIC NEPHRITIS AND EDEMA

Case 1 J K , a white male laborer aged 50, entered the hospital on June 1, 1926, with the following history He had always been in good health until about January 1, 1926, when he began to have severe morning headaches and his legs began to swell The swelling varied in intensity but never entirely disappeared On admission he was generally edematous The heart was normal The blood pressure was 180/110 Fundus examination Optic neuritis in both eyes, discs swollen, hemorrhagic spots, atrophic areas about macula Vessels tortuous The function of the kidney was greatly reduced Doubly refracting lipoids were found in the urinary sediment On July 2, uremia set in and he died the next day

Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules

Case 2 F P , aged 40 was admitted to the hospital on January 16, 1927, with the following complaint. Six weeks before, his face and legs became swollen to

such a degree that he was forced to quit his work. The blood pressure was 260/154. Aside from a moderate enlargement, the heart was normal. The lungs were normal, considerable ascites was present, the liver was palpable but not painful and the scrotal sac was filled with fluid. A few doubly refracting lipoids were found. The renal function was greatly reduced. Ophthalmoscopic examination. Discs markedly swollen and edematous. Retina had many hemorrhages. Veins were very tortuous and distended, it was impossible to see vessels throughout their course due to edema of retina. This patient left the hospital on the fourth day after entrance.

Diagnosis Chronic diffuse glomerular nephritis, with secondary lipid degeneration of the tubules.

Case 3 S. C., a negress, aged 24, entered the hospital on July 14, 1926, complaining of sore throat, violent headache, nausea, vomiting and dyspnea. She had had an attack of tonsillitis in 1922 after which edema, headache and bloody urine developed, and she was confined to bed for seven weeks. About July 19, 1926, she had another attack of sore throat, again followed by edema, vomiting and the other symptoms. Physical examination. She was well developed, considerably swollen, quite stuporous, and had a blood pressure of 210/130. Many doubly refracting lipoids were found in the urinary sediment. The renal function was reduced to a very low level. She went into uremic coma and died on August 10, 1926. Autopsy findings. A pair of white, coarsely granular kidneys were found, the right one weighing 56 grams, the left 75 grams. The capsule was adherent to the cortex and stripped with difficulty. The cortex was thinned. The cortex and columns of Bertini were pale with a tinge of yellow similar to that seen in pure lipid nephrosis. The peripelvic fat was less than normal. On microscopic examination many glomeruli were completely obliterated, others were partially destroyed by fibrous tissue proliferations. Extensive fibrosis was seen. In some areas there was an increase of cells, with exudate in the capsular spaces. With fat stains large quantities of fat were found in the tubular epithelium of the convoluted tubules and in the interstitial tissue. Some of the fat was anisotropic. The tubular epithelium was universally degenerated.

Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules.

Case 4 F. W., a white male, aged 36, a salesman, was seen for the first time on April 3, 1926. His chief complaints, general edema and headaches, were of several months standing. There was considerable edema of the entire body. The heart's action was normal. The blood pressure was 230/140. On polariscopic examination many doubly refracting lipoids were found in the urine.

Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules.

Case 5 F S, aged 34, a foreman in a factory, was first seen on May 9, 1926. He complained of generalized dropsy, severe occipital headaches, and epistaxis for the past three months. At the age of 19, he had an attack of scarlet fever, followed by acute glomerular nephritis, symptoms of which lasted for four months. He was quite well until three months before coming under observation. Physical examination. There was a generalized anasarca. The heart was enlarged to left. The blood pressure was 208/130 during the time he was under treatment. On every examination many doubly refracting lipoids were found in the urine. Renal function was greatly impaired. He died in uremia on June 14, 1926. Autopsy findings. The heart weighed 420 grams. There was a left ventricular hypertrophy. Both kidneys were larger than normal, the right one weighed 185 grams, the left 163 grams. Both were pale, the surfaces were mottled. On section the cortex was found thicker than normal and presented a fatty appearance, not unlike that seen in pure nephrotic cases. The capsule stripped easily though in places it was adherent to the cortex. Microscopically. A considerable increase in the fibrous tissue was found. Practically every glomerulus showed signs of inflammation. Hyaline necrosis of many capillary loops was found. The epithelial cells lining the convoluted tubules were swollen and many had undergone disintegration. With Scharlach R, large quantities of fatty material were found in the epithelial cells of the tubules, especially of the distal convoluted tubules. Some of this fat was found to be doubly refracting.

Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules.

Case 6 S S, a white female, aged 23, was seen for the first time on October 4, 1926. The chief complaints were swelling of the face and ankles and shortness of breath. On September 1, 1926, she began to have edema of the ankles and head ache. Physical examination. The edema about the eyes and ankles was well developed. The pulse was regular and full and the radial vessels were not thickened. The heart and lungs were normal. The blood pressure was 170/105. Doubly refracting lipoids were constantly present in the urine. Renal function was slightly decreased.

Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules.

Case 7 F K, a white male, laborer, aged 39, entered the hospital on June 30, 1925. Two months previous to entrance for the first time in his life he had swelling of the face and ankles. The edema gradually progressed to general anasarca. The heart and lungs were normal, the blood pressure was 185/110. Doubly refracting lipoids were found in the urinary sediment. Renal function was seriously impaired. There was no remission in the course of the disease, and on July 23, 1925 he died in uremic coma.

Diagnosis Chronic glomerular nephritis with secondary lipid degeneration of the tubules.

Case 8 J D , a boy aged 13, entered the hospital on November 6, 1925, with the following history About two weeks before entrance a sore throat developed with swelling of the lymph glands on both sides of the neck After two weeks edema of the face was noticed Within a few days there was a general anasarca The blood pressure was 118/60 Renal function was slightly reduced Many doubly refracting lipoids were found in the urinary sediment The edema disappeared gradually, the urine continually showed doubly refracting lipoids For the two years that this patient has been under constant supervision, doubly refracting lipoids have always been present in the urine At intervals the edema was developed with other findings of glomerular nephritis

Diagnosis Chronic glomerular nephritis with secondary lipid degeneration of the tubules

Case 9 S W , a white male, aged 42, laborer, was admitted to the hospital for the last time on December 4, 1925 He had been in the hospital a number of times since 1923 Chief complaint For the past four months he had been suffering from shortness of breath, pain in the back, headache and dropsy The dyspnea came and went, the edema, though it fluctuated in intensity, persisted throughout the illness The past history was unimportant The blood pressure was 210/140 The heart was greatly enlarged Renal function was moderately reduced, a hypercholesterolemia was present Autopsy findings The heart weighed 728 grams, the left ventricle was unusually hypertrophied The valves were practically normal Slight sclerosis of the aorta around the coronary ostia was present but the lumina were patent Fluid was found in the pericardial, peritoneal, and pleural cavities, general anasarca was present Both kidneys were slightly smaller than normal and red in color The right weighed 135 grams the left 129 grams The capsule stripped with ease, leaving a finely granular surface Some granules were composed of yellowish deposits On sections the cortex was thinner than normal, but the markings of the kidneys appeared normal Microscopically There was a selective tubular degeneration Stained with Sudan 3 fresh sections showed a fatty deposit confined to the proximal convoluted tubules and the collecting tubules Many of the convoluted tubules, both proximal and distal, contained doubly refracting lipoids Intracapillary as well as capsular glomerulitis was present The interstitial tissue was moderately increased Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules

Case 10 J Y , a white male, aged 29, was admitted to the hospital on January 18, 1927, complaining of swollen legs, arms, face and chest The trouble began one month before entrance to the hospital, he had no other complaint and had had no trouble of any kind before the onset of the present illness Other than for a soft mitral systolic murmur the heart was normal Ascites and general anasarca were present The eye grounds were normal The blood pressure was 145/95 Many doubly refracting lipoids found in the urine After one week the edema

disappeared and the patient felt very well. Diagnosis Chronic glomerular nephritis with secondary lipid degeneration of the tubules

Case 11 G K, a white male, aged 22, was admitted to the hospital on August 10, 1925 complaining of cough, shortness of breath and dropsy. About two months previous to admission to the hospital a generalized anasarca developed. Physical examination. Edema and dyspnea were present. The heart was normal. Radial vessels were normal. Some fluid was present in the abdominal cavity and in the scrotal sac. The lungs were normal with the exception of rales in both lower lobes. The blood pressure was 165/110. Many doubly refracting lipoids were found in the urinary sediment. Renal function was decidedly reduced. The eye grounds showed an aluminuric retinitis. He died in uremic coma on November 30, 1925. Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules

Case 12 F K, a white male, aged 55, entered the hospital December 22, 1926, complaining of shortness of breath, edema of face and legs and headaches. The edema although present on and off for the past year and one half had been persistent and considerably increased during the past three months. The heart was found to be moderately enlarged, and somewhat more rapid than normal, but otherwise was not abnormal. The blood pressure was 240/140. Palpation of the radial vessels revealed some thickening. No doubly refracting lipoids were found. The renal function was greatly reduced. He developed an asthenic type of uremic coma and died on January 18, 1927. Autopsy findings. The heart weighed 500 grams. The valves were normal. The left ventricular wall was increased in size. Both kidneys were greatly contracted, the right kidney weighing 41 grams, the left 64 grams. There was a most unusual coarseness to the surface of both kidneys. The capsule was removed with considerable difficulty and portions of the cortex adhered to the capsule. On sectioning, the peripelvic fat was increased. The cortex thinned and the demarcation between cortex and medulla was in places not clearly defined. Histologically, the glomeruli showed intracapillary as well as extra-capillary glomerulitis. Considerable interstitial fibrosis was seen. Arteriosclerosis was widespread. The tubular epithelium was gone in some places, in others greatly swollen and degenerated. With Sudan 3 a large amount of fat was found in the tubular epithelium, and many doubly refracting lipoids were found in the distal and proximal convoluted tubules. Diagnosis Malignant hypertension (renal type) with secondary lipid degeneration of the tubules

Case 13 J C, a white male, aged 40 years, entered the hospital for the first time on October 25, 1924, complaining of swollen legs and pain in the small of the back for five months. Physical examination. Generalized edema present. The heart was normal with the exception of a greatly accentuated aortic sound. Ascites was present, the scrotal sac was distended with fluid. Eye grounds exami-

nation showed a papillitis with hemorrhages in the right eye and to a lesser degree in the left. The blood pressure was 220/120. He left the hospital but re-entered on February 5, 1925. Doubly refracting lipoids were found in abundance in the urinary sediment. On December 15, 1925, he began to have uremic convulsions and died in uremic coma December 18, 1925. Autopsy findings (partial). The kidneys were larger than normal, the right one weighing 156 grams, the left 163 grams. The surface was smooth and there was a diffuse yellowish tinge throughout the cortex and columns of Bertini. The markings between the cortex and medulla were well preserved. Microscopically. Many doubly refracting lipoids were distributed rather evenly throughout the convoluted tubules, descending loops of Henle and in the interstitial tissue. None was found in the glomeruli. The glomeruli were universally diseased, an intra-capillary glomerulitis with swollen tufts characterized the picture, many glomeruli were fibrosed and hyalinized. The blood vessels appeared normal.

Diagnosis Chronic diffuse glomerular nephritis with secondary lipid degeneration of the tubules

Case 14 A L, a white female, aged 30, was first seen on October 6, 1926, complaining of edema, dizziness and headache. She had an attack of acute glomerular nephritis in 1921. She remained quite well from 1921 until the present attack came on. The heart was normal. The blood pressure was 220/110. The radial arteries were thickened. Renal function was reduced. A hypercholesterolemia was present. On January 29, 1927 uremic coma developed and she died the next day.

Diagnosis Chronic glomerular nephritis with secondary lipid degeneration of the tubules

GROUP II PATIENTS WITH CHRONIC NEPHRITIS AND NO EDEMA

Case 15 C G, a white male, aged 58, entered the hospital on February 5, 1927, on account of headache, cough, dizziness and great weakness. For two months previous to entrance he had been suffering from polyuria and headaches. On the day of entrance he began to have twitching about the mouth and arms. Uremic coma and a bilateral broncho-pneumonia developed. The heart was slightly enlarged. The radial vessels were thickened, tortuous, and calcified. The blood pressure was 180/112. There was no edema and no history of any. No doubly refracting lipoids found. Renal function greatly impaired. He died of uremia on February 7, 1927. Autopsy findings (partial). Both kidneys were surrounded by a mass of fat. They were smaller than normal—the right weighed 118 grams, the left 110 grams—and on peeling of the slightly adherent capsules a finely granular cortex was seen. On section, the cortex was found very thin in places, the interstitial tissue increased. The peripelvic fat was increased. Throughout the kidney as well as the hilum, the vessels were thickened and stood out prominently. Microscopic examination. The tubular epithelium was uni-

versally degenerated. Fat was found with Sudan 3 in the renal tubular epithelium and in the walls of many arterioles. No doubly refracting lipoids were found. Many glomeruli were completely obliterated, others were undergoing fibrosis and hyalinization. Glomerular crescents were numerous and fibrosis tissue proliferation around the capsules was prominent. A generalized arteriosclerosis was found.

Diagnosis: Chronic diffuse glomerular nephritis.

Case 16 P. A., aged 31, white female, was first seen on October 17, 1926. The chief complaints were severe headaches, blurring of vision, and loss of weight and strength with polyuria and nocturia. Except for scarlet fever at the age of eight the past history was negative. During September 1925, she was taken with severe headaches which would persist for days at a time. A few months later her vision began to be affected. Examination: The pulse was hard and a palpable whipcord radial was felt. The heart was moderately enlarged and the heart sounds were of good quality. The lungs and abdomen were normal. The blood pressure was 250/150. No doubly refracting lipoids were found. Renal function was gravely impaired. Eye ground examination showed an albuminuric retinitis. A fibrinous pericarditis developed on October 23, 1926. She died on October 25, 1926. No edema developed.

Diagnosis: Chronic diffuse glomerular nephritis.

Case 17 W. H., a white male, aged 52, entered the hospital on the first of December 1926, complaining of polyuria, visual disturbances, dyspnea, and headache. The present trouble began three months before entrance. Except for the fact that his father died of "Bright's disease" the family history was negative. He had had hypertension for 5 years. Physical examination: The patient was a thin muscular man who seemed very restless and distressed. The abdomen, genitalia, extremities and lungs were quite normal. The heart was enlarged, the left heart border was palpated $1\frac{1}{2}$ inches outside the left nipple line. The radial vessels were thickened but not calcified. The heart sounds were strong. There was no edema. The blood pressure was 188/126. Renal function greatly depressed. Ophthalmoscopic examination disclosed old as well as recent retinal hemorrhage. The vessels were sclerotic. He died of uremia on December 25, 1926. Autopsy findings: Both kidneys were contracted, the right one weighed 112 grams, the left 100 grams. The capsules stripped with difficulty, and left a finely granular surface. The peripelvic fat was not increased, the marking between the cortex and medulla was obliterated in places. The cortex was thinned. Histologically the glomeruli were all diseased, some showed evidence of recent and some of old inflammations. The arteriolar walls were unusually thickened in places. Complete atresia of the lumen was found. The tubules were uniformly diseased. Sections were stained for fat but none was present. No doubly refracting lipoids found.

Diagnosis: Malignant hypertension (renal type).

Case 18 C R , white male, aged 25, entered the hospital on October 23, 1926, complaining of dizziness, backache, polyuria, nocturia and weakness. He had always been well until the age of 19, when he suffered from chorea followed by endocarditis and pericarditis. He recovered within the year and continued to work until he was incapacitated by the present illness in October 1926. Examination. There was no edema. Blood pressure 190/116. He had a chronic adhesive pericarditis. No doubly refracting lipoids were found. Eye grounds were practically normal. Renal function was moderately reduced. The cholesterol was elevated.

Diagnosis Chronic diffuse glomerular nephritis

Case 19 R O , a white male, aged 50, was admitted into the hospital March 3, 1926, with dyspnea, edema of the lower extremities and ascites. He has been quite well until about January 1, 1926, when he was taken with shortness of breath, cough and dropsy. The edema here was considered to be the result of cardiac failure. The heart was excessively enlarged and a mitral systolic murmur was heard. No irregularity was present. There was considerable thickening of the radial vessel walls and some calcification was found. No doubly refracting lipoids found. Renal function was reduced. He died of pneumonia (lobar) October 16, 1926. Autopsy finding. The heart weighed 668 grams, the left ventricle was greatly hypertrophied. Old negative lesions involved the mitral valve. Coronaries more considerably thickened and calcified, partially occluding the orifices. Both kidneys appeared smaller than normal. The right weighed 142 grams, the left 154 grams. They were finely granular, in appearance the granules being irregular in size and gradually disappearing in the region of the pelvis, there was an occasional atrophic depression. On section the cortex was congested and close above several pyramids it exhibited a yellowish crescent-shaped thin area. The pyramids were pale. All the visible smallest blood vessels were stiff and gaping. The peripelvic and perirenal fat tissue was increased. Microscopically. No fat was found in the tubular epithelium. Many glomeruli were completely fibrosed, many others showed capsulitis and increase of intracapillary cells. Arteriolar walls were universally thickened. No doubly refracting lipoids found.

Diagnosis Malignant hypertension (renal type)

Case 20 A N , a white male, 42, entered the hospital on October 26, 1924. He complained of severe headaches, epistaxis, dizziness, vomiting and insomnia for the past four months. The blood pressure was 240/150. On ophthalmoscopic examination a disseminated choroiditis was found. The heart was enlarged, rapid, but regular in action. There was no edema. Kidney function was greatly reduced. Radial vessel walls uniformly thickened. No doubly refracting lipoids found. He died in uremic coma on January 11, 1925. Autopsy findings. The heart weighed 462 grams and left ventricle was exceedingly hypertrophied. Examination of the valves and coronary arteries revealed no abnormalities. Both kidneys were contracted and granular, and the capsule stripped with difficulty.

Right kidney weighed 125 grams, the left 118 grams. The cortex was very thin and there was an increase of fibrous tissue. Microscopically Many glomeruli were completely fibrosed, evidences of capsulitis and intracapillary glomerulitis were present. Hyaline necrosis of capillary loops found. In the lumen of the tubules were found many desquamated epithelial cells and blood cells. The tubular epithellum was diffusely degenerated. Considerable fat was found with Sudan 3 in the tubular walls in the interstitial tissue, and around the walls of arterioles. None of this fat was anisotropic.

Diagnosis Chronic diffuse glomerular nephritis

Case 21 R. McF, a white male, aged 52, was admitted to the hospital on July 26, 1926, complaining of headache, dyspnea and palpitation of the heart. Until the onset of the present trouble, he had always been well. Examination. Blood pressure 230/100. The heart was enlarged to the left, an apical systolic murmur transmitted to axilla was heard. There was no edema, the radial blood vessel walls were greatly thickened but no calcification was present. Ophthalmoscopic examination showed an increase in light reflex of the arteries, hemorrhages old and recent were present. No doubly refracting lipoids were found. The renal function was reduced. On December 16, 1926, he died of apoplexy. Autopsy findings. Unfortunately permission for examination of the brain was not given. The heart weighed 565 grams. Left ventricular hypertrophy was marked. Valves normal. Both kidneys were decidedly contracted and coarsely granular, the right one weighed 94 grams, the left 102 grams. By stripping away the capsule some portions of the cortex were removed. The peripelvic fat was greatly increased. In places the demarcation between cortex and medulla could not be seen, the cortex was remarkably thinned. Microscopically, many areas of cellular infiltration were seen, the glomeruli were greatly diseased, extra capillary glomerulitis was present, hyaline necrosis of many capillary loops found, extensive fibrous obliteration of glomerular vessel walls moderately fibrosed. No fat found in the tubules with fat stains, and no doubly refracting lipoids were found.

Diagnosis Chronic diffuse glomerular nephritis

Case 22 G. L., a white male, aged 36, entered the hospital on February 24, 1925, complaining of blurring of vision and vomiting and occipital headaches for the past month. At the age of 24 he contracted scarlet fever, which kept him confined to bed for eight weeks, but he said that he had no kidney trouble at that time. The patient was a thin anemic looking man without edema. The heart was enlarged to left, was regular in action and no murmurs were made out. The lungs, abdomen and genitalia were normal. The blood pressure was 185/100. No doubly refracting lipoids were found. The blood cholesterol was not elevated. There was a profound reduction in renal function. On February 28, 1925, four days after entrance a fibrinous pericarditis and uremia developed and he died. Autopsy findings. The heart weighed 315 grams, fibrinous pericarditis found. Both kidneys were surrounded by fat tissue that was firmly adherent to the upper

half of each organ. The right kidney weighed 149 grams, the left 155 grams. The surface of the kidneys was granular and the cortex thin. On section the cortex was congested. The capsule was thickened and adherent to the surface. Microscopic examination. The uriniferous tubules were compressed and many were destroyed. There was a cellular infiltration into the interstitial tissue. The Malpighian bodies varied greatly in size and shape. Many were hyalinized, others partially fibrosed. The tubules contained both red cells and leukocytes and in places organized casts. No fat was present in the tubular epithelial cells. No doubly refracting lipoids found.

Diagnosis. Chronic diffuse glomerular nephritis.

Case 23. L. J., a white male, aged 32, was admitted to the hospital on November 11, 1925, complaining of headache. The blood pressure was 240/150, the heart was slightly enlarged, otherwise normal. No edema was present. Ophthalmoscopic examination revealed old retinal hemorrhages but no recent one. No doubly refracting lipoids present. Renal function was greatly decreased. He was under observation until death in September 1926. Edema never developed. Uremia with plastic pericarditis terminated the course of the disease on September 15, 1926. Autopsy findings. The heart weighed 318 grams, the left ventricular wall was greatly hypertrophied. Plastic pericarditis present. Right kidney weighed 62 grams, the left one 55 grams. The capsules were adherent to the cortex. Both kidneys were coarsely granular in type. The cortex was very thin and in places the demarcation between cortex and medulla was obliterated. Microscopically, the fibrous tissue throughout the kidney was increased. A capsular as well as an intracapillary glomerulitis was universal. Areas of cellular infiltration numerous. The tubules showed evidence of degenerative changes. No doubly refracting lipoids present, and no fat was found with fat stains.

Diagnosis. Chronic diffuse glomerular nephritis.

Case 24. D. D., a white female, aged 47, entered the hospital on January 17, 1927, complaining of dyspnea, cough, headache and vomiting for the past year. The blood pressure was 205/142, the heart was enlarged to the left and rapid. The radials were thickened but not calcified. Renal function was greatly reduced. No doubly refracting lipoids found. Coma developed and she died on February 2, 1927. Autopsy findings. The heart weighed 308 grams. There was a remarkable hypertrophy of the left ventricular wall. The coronary arteries were patent, but moderate sclerosis was found. Both kidneys were coarsely granular and contracted, the right one weighed 105 grams, the left the same. The capsule stripped with considerable difficulty. On section the cortex was thinned and an increase in interstitial tissue could be seen. The walls of the smaller vessels were thickened and stood out prominently. Microscopically. Practically every glomerulus was diseased. Many had undergone complete fibrosis, extensive capsulitis as well as intracapillary inflammation was seen. Areas of cellular increase were numerous. The epithelium of the tubules was extensively degenerated. Moder-

ate amount of fat was found with Sudan 3 in the epithelium of the convoluted and straight tubules. No doubly refracting lipoids found.

Diagnosis Chronic diffuse glomerular nephritis

Case 25 M J, a white female, aged 40, entered the hospital on January 28, 1927, complaining of nervousness, visual disturbances and nocturia. The heart was enlarged. The walls of the radials were practically normal. The blood pressure was 260/136. There was no edema. No doubly refracting lipoids found. Autopsy findings: There was no cerebral hemorrhage. Both kidneys were very small and hard in consistence. The right weighed 75 grams, the left 83 grams. Their surface showed a diffuse granular appearance, the granules being regular in size and less pronounced toward the hilus of the organs. On the cut surface the cortex appeared thin, the vessels were gaping. The peripelvic fat tissue was increased. Microscopically: The glomeruli in places showed an increase in the number of nuclei and thickening of the Bowman's capsule, in places the glomeruli were completely fibrosed. A diffuse round cell infiltration of the interstitial tissue was found. No fat found with fat stains and no doubly refracting lipoids found.

Diagnosis Chronic diffuse glomerular nephritis

GROUP III. PATIENTS WITH HYPERTENSIVE CARDIOVASCULAR DISEASE WITH CARDIAC EDEMA

Case 26 D N, a white male, aged 51, was first examined on October 2, 1925. He had been complaining of headaches, dyspnea and swollen ankles for the past year. The radial arteries were considerably thickened, tortuous, and hard to compress. The left heart border was found in the anterior axillary line. There were no murmurs nor evidences of fluid. The aortic second sound was greatly accentuated. A tendency to gallop rhythm was present. Blood pressure 215/124. Examination revealed extensive edema, ascites, pleural effusion and some pericardial effusion. No doubly refracting lipoids were found on many examinations.

Diagnosis Hypertensive cardiovascular disease.

Case 27 M G, a white female, aged 54, entered the hospital on July 8, 1926, complaining of precordial distress, dyspnea, swollen arms and legs. The trouble began five years previously when shortness of breath and weakness caused her to give up her occupation. The blood pressure, at that time, she said was over 200. The radial artery walls were greatly increased in thickness and were tortuous. Ascites was present with generalized edema. The heart was greatly enlarged and the sounds were muffled, weak and rapid. The blood pressure was 242/130. The condition of the patient remained about the same, except for short periods of improvement until she died of heart failure on September 5, 1926. Autopsy findings: The heart weighed 585 grams. The walls of the left ventricle were greatly thickened. The mitral valve was not of an old rheumatic endocarditis. The

right kidney weighed 128 grams, the left 122 grams Both kidneys were coarsely granular in appearance, and were contracted The capsule was slightly adherent On section the cortex was found quite thin and the interstitial connective tissue was increased The normal markings of the kidneys were practically obliterated Many of the larger and smaller arteries stood out conspicuously and their walls were unusually thickened The peripelvic fat was abnormally increased Microscopically, many glomeruli were normal, others enlarged, while some were completely fibrosed Hyalin degeneration of the intima of many of the smallest arterioles was found with many glomeruli partially hyalinized and fibrosed With Scharlach R, some fatty material was found scattered throughout the epithelial cells of many of the convoluted and straight tubules None of this fat was found to be doubly refracting

Diagnosis Hypertensive cardiovascular disease

Case 28 W H, a white male, aged 48, entered the hospital on February 12, 1926 His blood pressure had been elevated for the past year, but the present trouble began a month before entrance He was dyspneic, orthopneic, edematous and cyanotic The walls of the radial arteries were extensively thickened, and felt like solid cords to the palpating fingers Blood pressure 210/106 The left ventricle was exceedingly hypertrophied The heart sounds were distant and weak A systolic mitral murmur was present Chronic hypertrophic emphysema as well developed Edema of the extremities as well as ascites was present Renal function was depressed No doubly refracting lipoids were found in the urinary sediments Improvement followed treatment

Diagnosis Hypertensive cardiovascular disease

Case 29 J M, a white male, aged 50, entered the hospital on February 15, 1926 He had known that his blood pressure was over 200 for the past three years and that the urine had been free from albumin About two months before entrance he began to have swollen legs and was dyspneic The walls of the radials were considerably thickened and tortuous, but no calcification was found There was an enormous scrotal edema, as well as extensive edema of the lower extremities On examination the left heart border was found well outside the nipple line Some irregularity of rhythm was present, and the heart sounds were muffled due to accumulation of pericardial fluid Renal function was moderately reduced Examination of the urinary sediment with the polaromicroscope occasionally revealed a few doubly refracting lipoids

Diagnosis Hypertensive cardiovascular disease

Case 30 B M, a white male, aged 46, entered the hospital on January 8, 1927 In 1917 when examined for army service he was refused admission because the blood pressure was over 200, and his heart was enlarged He had very little trouble until November 1926 when his feet began to swell and dyspnea set in These symptoms steadily progressed until he came to the hospital Blood pressure

218/100 The walls of the radial were definitely thickened, but no tortuosity or calcification made out The left side of the heart was greatly hypertrophied There was considerable edema of the lower extremities with a moderate degree of scrotal dropsy No ascites was present Renal function was reduced. No doubly refracting lipoids were found Although heart failure was pronounced he died suddenly on May 19, 1927 of pulmonary embolism Autopsy findings The heart weighed 613 grams No valvular disease present Aorta widened otherwise normal Thrombi were found in the right auricular appendage An embolus was found in a branch of the left pulmonary artery Both kidneys were enlarged and smooth The right weighed 198 grams the left 186 grams The capsule stripped easily On section the cut surface seemed normal except that the wall of many small arteries were seen to be thickened Histologically, many glomeruli were completely fibrosed, others partially fibrosed and bivalvized The tubular epithelium was swollen in places The walls of smaller arterioles were excessively thickened and lumen of some was almost occluded With fat stains no fatty material was seen No doubly refracting lipoids were found

Diagnosis Hypertensive cardiovascular disease

Case 31 L D, a white female, aged 44, had had high blood pressure and shortness of breath for the past year She entered the hospital on November 7 1926 with pronounced general anasarca and dyspnea The walls of the radial and other accessible arteries were very thick There was considerable cardiac enlargement to the left Blood pressure 196/115 Some free fluid was found in the abdomen and in both pleural cavities No doubly refracting lipoids found in the urine Renal function was reduced She died of heart failure on March 3, 1927 Autopsy findings The heart weighed 497 grams Evidences of an old endocarditis were found on the mitral valve and aortic valves Both kidneys were contracted, the right weighed 112 grams, the left 107 grams The capsule stripped with some difficulty, leaving a finely granular surface On section the peripelvic fat was found greatly increased The cortex was thin and the interstitial connective tissue was increased to such degree that the marking between cortex and medulla was hard to make out Many of the smaller arteries stood out, it could be seen that their walls were greatly increased in thickness Microscopically, many glomeruli were hypertrophied and the lumens of the tubules in places were widened There was a definite fibrosis of many of Bowman's capsules and many glomeruli were obliterated by connective tissue Other glomeruli were normal The tubular epithelial cells were swollen but otherwise normal The chief finding was the extensive thickness of the smaller blood vessel walls with atresia of their lumen in places With Scharlach R, a small amount of fatty material was found in the epithelial cells of a few of the convoluted and straight tubules also some was found in the intertubular tissue None of this fat was doubly refracting

Diagnosis Hypertensive cardiovascular disease



FIG I CASE 3 LEFT KIDNEY (NATURAL SIZE), SHOWING THE UNIFORMLY GRANULAR SURFACE AND CONTRACTION OF THE ORGAN



FIG II CASE 3 AREA SHOWING EXTENSIVE DEPOSITS OF LIPOID SUBSTANCES
IN THE TUBULAR EPITHELIUM AND TO A LESSER EXTENT IN THE INTER
STITIAL TISSUE, SECTION STAINED WITH SUDAN III, $\times 700$

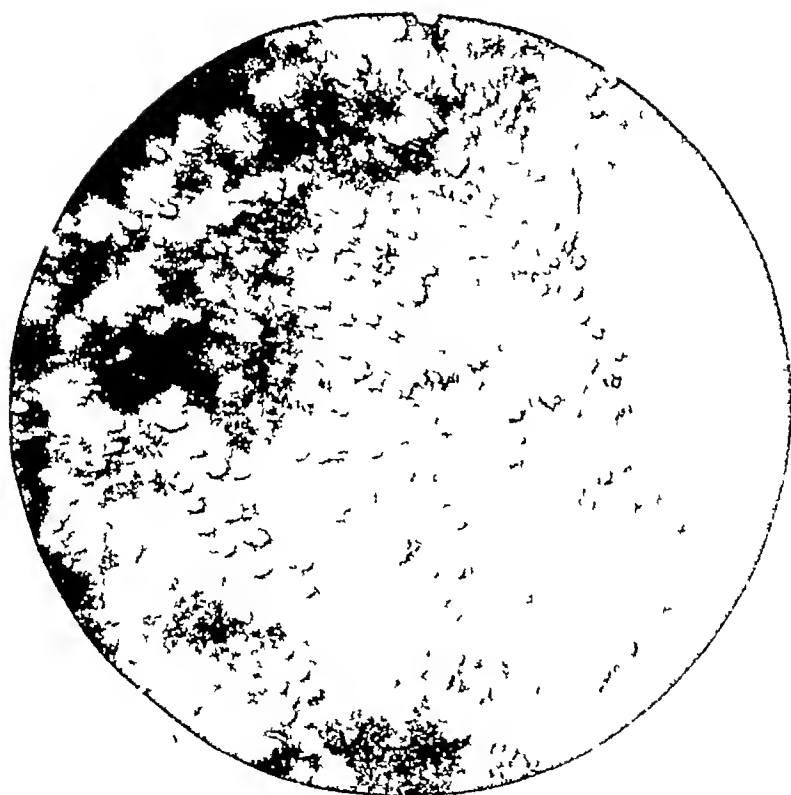


FIG. III CASE 3 SECTION OF AN AREA SIMILAR TO THAT IN FIGURE II

The tissue is unstained and observed under crossed Nicol's, the doubly refracting substances (lipoid) are in both the tubular cells and the interstitial tissue, $\times 700$



FIG IV CASE 9 UNSTAINED SECTION OBSERVED UNDER CROSSED NICOL'S,
SHOWING THE SELECTIVE LOCALIZATION OF THE DOUBLY REFRACTING SUB-
STANCES (LIPOID) IN CERTAIN PORTIONS OF THE TUBULES, $\times 375$

THE BLOOD URINE UREA CONCENTRATION RATIO IN HYPERTENSION

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The blood urine urea concentration ratio, following the work of MacLean (1), Harrison (2), Addis (3), Rabinowitch (4, 5, 6, 7) and Van Slyke (8, 9), has been determined in a series of 44 patients with vascular hypertension. They are arranged in three groups (tables 3, 4 and 5) of increasing severity of cardiovascular damage. They are not considered to have a primary nephritis, the extent of secondary renal damage was unknown.

METHODS

Following the plan of Rabinowitch our procedure was as follows:

1. No food or fluids after 9:00 p.m.
2. Two grams of soda bicarbonate at 6:00, 7:00 and 8:00 p.m.
3. At 9:00 a.m. (a) bladder emptied (specimen saved), (b) blood drawn, (c) phenolsulphonephthalein injected intravenously, (d) 15 grams of urea in 500 cc. of water by mouth (other workers use 150 cc. of water).

Urine collected at 10:00 and 11:00 a.m., 12:00 and 1:00 p.m. (no food or fluids during this period).

5. Blood drawn at 10:00 a.m. and 1:00 p.m.

The determinations made on these specimens are the volume and specific gravity, including the fasting specimen of urine, the phenolsulphonephthalein percentage and the concentration of urea in the urine of the second hour. This last is done by the usual aeration nesslerization method. The blood urea nitrogen is determined in the three blood specimens by the new mercury titration method of Hensch (10). The urea concentration factor is obtained by dividing the urea value in milligrams per 100 cc. of urine of the second hour by the average of the urea in milligrams per 100 cc. of blood in the fasting and first hour blood specimens. The reliability of the urease nesslerization technic used for the urine determination is well known. The observations of the English investigators would seem unreliable in view of the recognized faults in the hypobromite method which they use. The technical work is greatly shortened by employing

TABLE 1
Urea nitrogen in milligrams per 100 cc of blood

Standard (Van Slyke technic)	Hench (titration technic)	Difference
mg	mg	mg
14 7	16 0	+1 3
13 5	12 0	-1 5
16 1	14 0	-2 1
20 4	18 0	-2 4
13 2	14 0	+0 8
14 8	16 8	+2 0
15 1	14 8	-0 3
17 1	16 4	-0 7
13 5	11 2	-2 3
11 1	15 6	+4 5
10 2	14 2	+4 0
13 9	13 5	-0 4
32 0	28 0	-4 0
26 4	22 4	-4 0
Average difference		± 2 16

TABLE 2
Normal

Name	Phthalain (intravenously) percent age in - hours	Fasting blood urea nitrogen (normal 20)	Fourth hour blood urea nitrogen* re turn within 10 of fasting	Urea concentration factor	Clinical diagnosis
A W B	65	14	19	57	Anemia
J G	75	15	21	44	Fracture
B McQ	70	20	24	30	Arthritis
O N	55	11	17	33	Hand injury
O N		13	24	35	Hand injury
J R		21†	23	34	Nerve injury
F S	75	14	15	48	Postoperative hernia
R W	60	23	25	25	Hand injury
Dr H	65	13	16	35	Hand injury
T C	70	16	24	28	Hand injury
B H	65	13	23	47	Neurosis
R B	70	18	22	27	Normal
M P	60	19	24	33	Duodenal ulcer
B A	65	20	32	21	Neurosis

* Following the work of Archer and Robb on urea tolerance

† Emphasized figures are abnormal

the mercury titration method recently developed by Hench. He has published comparative results. Our series of comparisons is given in table 1. The greatest difference is 4.5 mg. of urea nitrogen or 9.6 mg. of urea. (The average is 2.16 mg. of urea nitrogen or 4.6 mg. of urea.) This would usually make no serious change in the urea concentration factor as calculated but if the average error occurred in the same direction in both determinations, the false urea concentration factor would then be 2.5 points from the true value. Clinical estimations will certainly not require urea concentration factor of greater accuracy than this. In its present form the urea concentration factor range of error is probably 10 points owing to the unmeasured effect of diuresis.

RESULTS

In table 2 the data on 13 normal patients are given. The normal range of urea concentration factor by this procedure should thus be from 25 to 60, rejecting the one reading 21 as being influenced by some diuretic factor.

In table 3 the data from the group of 22 patients with mild vascular disease are given. These patients are all active and have very slight disability. They carry systolic blood pressures of from 170 to 200 mm. Hg, the diastolic is in the neighborhood of 100 mm. Hg. There is more or less cardiac involvement. They do not have edema or unusual polyuria. There is little, if any, urinary evidence of nephritis. There is no gross evidence of heart failure in these patients. They are representative of that large group of people in whom hypertension is gradually leading to degenerative changes in the heart, brain, and kidneys, from which they will eventually die. It is in this type of case that it would be most valuable to be able to measure the extent of kidney damage and it is in this type of case that the usual renal tests are inadequate. Brief histories of two such patients follow.

Miss E. W., a school teacher, aged 68, active, only complaint severe and intractable hives. Physical examination: old goiter, infected tonsils, heart enlarged, left heart border 11 cm., lungs negative, abdomen negative, no edema. Blood pressure 220/80, red blood cells 4,090,000, hemoglobin 47 per cent, urine entirely negative, basal metabolic rate -5 per cent, pulse 60, weight 130, positive Graham Cole test, van den Bergh 0.2 mg.

Dr L. F., aged 43, an active surgeon, admitted because of gall-stone colic. Later he was operated upon and returned to work. Physical examination: overweight, infected tonsils, lungs clear, no edema, heart enlarged, regular, no

TABLE 3

Clinically mild vascular disease—slight or no cardiovascular symptoms, no evidence of heart failure, no gross edema, no isosthenuria

Name	Phthalein (intravenously) percentage in 2 hours	Fasting blood urea nitrogen (normal 20)	Fourth hour blood urea nitrogen return with in 10 of fasting	Urea concentration factor	Clinical diagnosis
J J C	65	13	15	63	Essential hypertension, age 22, blood pressure 185/110
M R	65	26	32	28	No symptoms, age 26, blood pressure 150/90
F H	25	18	26	33	Slight symptoms, age 24, blood pressure 170/90
F B E		14	27	29	Mild arteriosclerosis, blood pressure 168/110
G F	50	13	22	22	Obesity, arthritis, blood pressure 200/110
L F	60	15	18	39	Cholecystitis, blood pressure 190/118
G I	55	21	27	32	Uterine tear, blood pressure 170/98
M M	20	16	31	43	Hypertension, blood pressure 200/110
S S	60	24	37	22	Intus, blood pressure 180/108
R B	50	19		24	Puerperal headaches, blood pressure 178/110
S R	50	15	21	26	Headaches, blood pressure 194/112
J S	60	21	23	32	Senility, prostatic obstruction, blood pressure 196/90
H B	60	26	35	32	Weakness, anemia, blood pressure 200/98
L S	60	23	32	24	Melancholia, hypertension, blood pressure 218/124
E W	75	22	35	15	Hives, cardiac hypertrophy, blood pressure 200/80
C L	65	26	56	13	Arthritis, blood pressure 196/110
J J C	60	16	28	22	No symptoms, blood pressure 200/110
R W H		14	28	33	No symptoms, blood pressure 190/98 158/80
S R	55	21	27	27	Effort syndrome, blood pressure 184/100
E W	45	22	28	30	Tired, hives, blood pressure 198/110
E D	40	19		11	Tired, cholecystitis, blood pressure 200/100
M F	45	19	26	27	Arteriosclerosis, glycosuria, blood pressure 155/68

murmurs, gall bladder tenderness Blood pressure 220/130, later 188/118 and 160/110, urine contained slight trace of albumin, no casts, red blood cells 4,240,000,

TABLE 4

Severe vascular disease—marked cardiovascular symptoms no gross edema except for one case with heart failure no isosthenuria

Name	Pythalein (intravenous) percentage in 2 hours	Fasting blood urea nitrogen (normal 20)	Fourth hour blood urea nitrogen return with in 10 of fasting	Urea concentration factor	Clinical diagnosis
T L A	65	12	28	27	Angina, senility blood pressure 218/96, died—cerebral hemorrhage
C L H	60	9	12	14	Coronary thrombosis, blood pressure 100/60
S L	30	17	34	29	Heart failure blood pressure 154/110
A. von H	70	22	29	25	Arteriosclerosis heart block, blood pressure 182/86
S W	55	16	24	17	Angina, blood pressure 220/120
C M G	60	23	34	8	Uremic headache nocturia, blood pressure 180/105
L. H	50	22	34	21	Auricular fibrillation, blood pressure 240/140
L. H	40	48	67	16	Hemiplegia blood pressure 238/132, death
H. R	50	26	28	21	Angina, vertigo blood pressure 180/110 died suddenly
M. R	45	18	28	16	Cerebral thrombosis blood pressure 204/120
H B	60	26	33	13	Hypertension, dyspnea, headaches, blood pressure 210/120
J B	45	28	40	27	Arteriosclerosis cerebral thrombosis, blood pressure 150/80
J A	65	24	29	24	Hypertension, gallop rhythm, blood pressure 170/120
T G E	35	26	34	19	Retinitis gallop rhythm, blood pressure 200/130
I N W	35	28	45	16	Hypertension with nephritis with edema blood pressure 270/158

white blood cells 6,400, hemoglobin 80 per cent, Wassermann test negative, stools normal, electrocardiogram normal, van den Bergh 2.9 mg

The phenolsulphonephthalein results in this series are all high normal with the exception of five. The fasting blood urea nitrogen is often very slightly elevated but not sufficiently to indicate definite azotemia. Of the twenty-two there are 13 urea concentration fac-

TABLE 5
Extreme vascular disease

Name	Phthalein (intravenously) percentage in 2 hours	Fasting blood urea nitrogen (normal 20)	Fourth hour blood urea nitrogen return with in 10 of fasting	Urea concentration factor	Specific gravity low and high	Clinical diagnosis
J F	60	12	19	28	1 008 1 017	Malignant hypertension, retinitis, age 32, blood pressure 222/158
I A	55	11	21	14	1 009 1 030	Malignant hypertension, cerebral hemorrhage age 34, blood pressure 220/120
M D	60	16	15	18	1 008 1 022	Malignant hypertension, angina, age 35, blood pressure 260/150
A L	40	20	21	18	1 015 1 020	Hypertension, cardiac decompensation, blood pressure 220/120

Fixation of specific gravity

N L	15	65	81	9	1 008 1 010	Final stage nephritis, decompensation, blood pressure 228/140, death
R P	30	32	35	3	1 007 1 010	Final stage nephritis, edema, blood pressure 184/130, death
E LaT	20	36	53	7	1 007 1 010	Malignant hypertension, blood pressure 270/140, death
C R E	10	42	46	12	1 010 1 010	Malignant hypertension, blood pressure 200/120, death

tors below 30, of these, 8 are definitely abnormal, i e., below 25. Two are below 20.

In table 4 the data on 14 patients with severe vascular disease are shown. In these patients the systolic blood pressure is frequently

over 200, the diastolic frequently over 110. The extent of vascular damage is evidenced by angina, coronary thrombosis, heart block, auricular fibrillation, cerebral thrombosis, and headache. There is one case with cardiac decompensation. Brief histories of two such patients follow.

Mr O, aged 57, gradual onset of right hemiplegia with associated aphasia. Physical examination: lungs clear, heart—left hypertrophy, regular, right arm and leg partially paralyzed, no edema, vessels of fundi sclerotic. Blood pressure 204/120, later 192/106, urine contains trace of albumin, occasional granular cast.

Mrs W, aged 60. Dull aching in left chest during exertion, stops immediately on resting, no dyspnea, no edema. Physical examination: lungs normal, heart—concentric hypertrophy, abdomen normal, pelvis normal. Blood pressure

TABLE 6
Nephritis without hypertension

Name	Phthalein (intra-venously, percent age in 2 hours)	Fasting blood urea nitrogen (normal 20)	Fourth hour blood urea nitrogen (normal within 10 of fasting)	Urea concentration factor	Clinical diagnosis
K. K.	55	20	40	25	Acute parenchymatous nephritis, blood pressure 125/85
M. K.	45	25	33	15	Cystitis syphilis, blood pressure 118/68
E. F.	0	157	191	7	Hydronephrosis (bilateral), isosthenuria, blood pressure 124/78, death

218/118, 222/120. Urine negative, basal metabolic rate -5 per cent, blood urea nitrogen 19.6, red blood cells 4,210,000, white blood cells 6,700, hemoglobin 86 per cent, Wassermann test negative.

Of the fourteen cases only three have phenolsulphonaphthalein results of clinical significance. These are 30, 35, and 35 per cent. In six cases the urine contains little albumin, in the others it contains much albumin and some casts. There is no correspondence between the phthalein percentage, the urea concentration factor and the amount of albumin. In nine there is a slight increase of the fasting blood urea nitrogen. In all fourteen the urea concentration factor

is less than 30 and in ten it is less than 25, of these it is less than 20 in seven cases

In table 5 the results from a series of patients with extreme hypertension are given. One early case in a young man and one case in the terminal stage are described.

TABLE 7
Correlation of change of urea concentration factor to volume

Name	Table where other data are shown	Urea concentration factor			Difference		Volume	
		A	Interval	B	Urea concentration factor	$\frac{V}{W}$ UCF	A	B
Mr L	4	12 (15)	1 week	29* (7)	+17	-8	160	60
I A	5	14 (24)	11 months	25 (6 6)	+11	-17	180	40
H B	3	23 (24)	2 months	32 (7 4)	+9	-16	70	35
A L	5	11 (17)	10 months	17 (4)	+6	-13	230	55
J B	4	27 (6)	3 months	31 (8)	+4	+2	50	70
Mrs K	6	15 (21)	1 month	19 (29)	+4	+8	120	140
J A	4	20 (31)	2 weeks	24 (34)	+4	+3	200	160
O N	2	33 (33)	1 month	35 (35)	+2	+2	80	130
Mr B	4	13 (24)	2 months	14 (4)	+1	-16	290	70
E W	3	15 (29)	1 month	15 (29)	+0	+0	230	225
Mr L	4	12* (15)	1 week	13 (14)	+1	-1	160	110
J J C	3	55 (13)	11 months	63 (18)	+8	+5	70	45
I H	4	14 (20)	3 months	21 (31)	+7	+11	120	130
S S	3	22 (31)	10 months	26 (61)	+4	+30	100	280
B B'		18 (22)	2 weeks	21 (33)	+3	+11	85	125
S R	3	18 (4)	6 months	26 (23)	+8	+19	60	130
Average of differences					±5 3	±10 2		

Figures in parenthesis = Our UCF $\times \sqrt{\text{Volume given} \div \text{Weight in kilograms}}$

* During acute decompensation urea concentration factor 29, when improved 1 week later urea concentration factor 12, third urea concentration factor still later 13

Dr J F, aged 32, a dentist, was known to have had gradually increasing hypertension for six years, at first very mild, later extreme. Complained of headaches and nervousness, later, visual disturbance. Physical examination: lungs clear, heart enlarged, aortic second accentuated, abdomen and extremities normal, no edema. Blood pressure 226/160, urine-albumin ++ and +++, occasional granular cast, red blood cells 4,200,000, white blood cells 9,100, hemoglobin 90 per cent, spinal fluid and blood Wassermann negative. Fundi showed albuminuric retinitis.

Mr LaT, aged 50, high blood pressure known for nine years. Complained of no pain or inability to continue his work as usual, no nocturia, slight edema of ankles. Lungs clear, heart much enlarged. Blood pressure 270/140 and 295/170, urine—albumin ++, occasional granular cast, fixed specific gravity, Wassermann test negative.

Of the eight cases five have definitely depressed phthalein readings. In those cases with renal insufficiency, as indicated by azotemia, there is definite isosthenuria. In this whole group the urea concentration factor is less than 30 and all but one are below 20, three are 10. It is interesting to note that those patients whose urea concentration factor was approximately 10 or below have died.

In table 6 the data of three patients having nephritis without hypertension are given. A correspondence with the clinical severity is evident.

In contrast, however, with this general parallelism with the degree of vascular disease there are occasions when very low figures are obtained which certainly do not represent the clinical condition. Thus, the specific gravity of the urine may be low and the urea concentration in the neighborhood of a few tenths of a per cent, while the blood figure is not unusual, the result is a very low factor. This happened definitely three times in a total of eighty-three urea concentration factor determinations but it is probable that the factor is often several points too low as judged by clinical criteria. Furthermore, as regards prognosis serious vascular accidents may, of course, occur with relatively good kidney function as indicated by this factor.

To determine the constancy with which this crude procedure would give checks it was repeated whenever possible. Table 7 presents 17 duplicates. In most instances the checks are remarkably good. The greatest differences, 11 and 17, are probably due to a change in circulation. Other differences may well correspond to an actual change in renal function. The average difference, including the two factors distorted by gross circulatory disturbances is plus or minus five. Even with this range of error the results are of clinical value in helping to grade the renal damage in patients with vascular hypertension into, roughly, three divisions, mild or negligible, moderate, and severe.

In table 7 a correlation between the change of urea concentration

factor and the change of volume in these successive tests is presented. Concerning these seventeen duplicates, inspection of the table indicates that where the second volume increased, as was true in six instances, the urea concentration factor also increased, i.e., contrary to what would be expected from simple dilution of the urine. When the volume decreased, as was true in eight, including the instance before and after decompensation, the urea concentration factor increased on an average eight points. Hence, no constant influence of change of volume is found. A check of successive urea concentration factors to four points or less occurs in nine instances. In these the changes in volume are from 70 to 290 cc, from 100 to 280 cc, from 200 to 160 cc, from 80 to 130 cc, from 230 to 225 cc, from 160 to 110 cc, from 120 to 130 cc, from 50 to 70 cc, and from 85 to 125 cc. Thus a very marked change in volume may not significantly change the urea concentration factor. It would, therefore, seem incorrect to uniformly modify the urea concentration factor by the volume. When our factor is multiplied by the square root of the quotient volume over weight of the patient in kilograms, the correspondence between the resulting modified factors is much less close than when the simple urea concentration factor is used and they would frequently indicate a change in renal condition which the clinical findings do not support and which the simple factors do not suggest. Modified factors, $UCF \times \sqrt{\frac{V}{W}}$, are shown in parentheses after each simple factor in table 7.

CONCLUSION

This procedure for measuring the ability of the kidney to concentrate urea is of clinical value. It seems possible by this means roughly to estimate that the degree of renal damage in hypertension is either negligible, moderate, or severe. A method of controlling the influence of water metabolism and excretion on the final result would very much increase the quantitative significance of the test.

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THE OXYGEN SATURATION OF HEMOGLOBIN IN THE ARTERIAL BLOOD OF EXERCISING PATIENTS

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The following data are presented at the present time even though they are incomplete, since circumstances necessitated an interruption of the work

Observations of Himwich and Barr (1) on the variations in oxygen content and oxygen capacity which occurred in the arterial blood of normal individuals as a result of exercise indicated that the oxygen saturation of the hemoglobin was increased by moderate exercise of short duration. If, however, the exercise was continued to the point of exhaustion, the saturation of hemoglobin might diminish. A similar decrease was noted by Harrop (2) in a convalescent subject, and also in three patients with polycythemia vera (3). A lessened saturation was found by Barcroft and others (4) when exercise was performed at high altitudes.

An explanation of these varying results was attempted. Though the saturation of hemoglobin in the lungs is influenced by many factors, it is in the last analysis determined by two only, the amount of oxygen diffusing through the pulmonary membrane and the volume of blood flow in the pulmonary circuit, the degree of saturation varying directly with the total amount of oxygen diffusing and inversely with the volume of the circulation. It was proposed that in moderate exercise of normal individuals, at sea level, the amount of oxygen diffusing is more than sufficient to compensate for the increasing circulation rate. However, when the exertion is of an exhausting character, the volume of blood flow may increase to an extent proportionately greater than the increase in oxygen diffusion. It is the purpose of this study to follow the variations in the saturation of

hemoglobin occurring in the lungs when the various factors involved in the process are changed by disease

EXPERIMENTAL

The present report is concerned with the response of several abnormal individuals to exercise. Nine patients were studied, one with

TABLE 1

Oxygen content, oxygen capacity, and saturation of hemoglobin, before, during and after short periods of exercise in patients

Disease	Patient	Date	Oxygen content of arterial blood		Oxygen capacity of arterial blood		Percentage saturation of hemoglobin	
			Before exercise	After exercise	Before exercise	After exercise	Before exercise	After exercise
Diabetes	{ William R. William R	October 31, 1922	17.4	19.1	18.3	21.1	95	90
		November 16, 1922	19.3	21.1	20.6	21.5	94	98
Anemia	{ John O'R John O'R Antonia O Patrick M Patrick M	July 26, 1923	15.0	15.3	15.6	17.1	96	89
		August 2, 1923	16.1	16.6	17.0	18.2	95	91
		August 29, 1923	8.7	9.7	9.1	10.5	96	92
		July 31, 1923	6.1	5.5	6.3	6.3	97	87
		August 7, 1923	5.6	4.8	5.6	6.1	100	79
Cardiac	{ Tony G Tony G	August 10, 1923	17.7	18.7	19.3	20.7	92	90
		August 20, 1923	17.8	18.3	18.5	21.3	96	86
Emphysema	{ William Ru Joseph B John L	July 19, 1923	20.3	21.3	21.4	22.5	95	95
		August 8, 1923	19.5	19.7	20.3	21.6	95	91
		August 9, 1923	17.5	5.2	22.4	22.6	78	23
Tuberculosis	Santos C	August 3, 1923	12.5	12.3	13.2	14.6	93	84

diabetes, three with anemia, one with auricular fibrillation before and after the normal heart rhythm had been restored by quinidin, three with varying degrees of emphysema and one with chronic pulmonary tuberculosis and secondary anemia. In all, thirteen observations were made. Protocols of the analyses and case records may be found at the end of the paper. The procedures and technique were similar to those employed in the experiments of Barr, Himwich and Green.

(5) All work was done on a bicycle ergometer about four hours after a light breakfast. One brachial artery was punctured about two minutes before exercise, the other about an equal length of time after the work was completed. The blood was analyzed for oxygen content and capacity by the method of Van Slyke and Stadie (6). The error of the method is 0.5 volumes per cent. The results are given in table 1.

Diabetes The two observations were done incidentally in the course of other work and are mentioned as evidence concerning the reaction of debilitated individuals to exertion and not in any sense as examples of a specific effect of diabetes. In William R. there was no

TABLE 2

Oxygen content, oxygen capacity and saturation of hemoglobin before, during and after short periods of exercise in normal individuals

Subject	Date	Oxygen content of arterial blood			Oxygen capacity of arterial blood			Percentage of saturation of hemoglobin		
		Before	During	After	Before	During	After	Before	During	After
	1922									
D. P. B.	August 8	19.7		21.4	20.5		21.5			
H. E. H.	August 10	18.0	19.7	19.7	19.1	20.0				
D. P. B.	August 15	19.9		22.7	21.3					
D. P. B.	October 17	20.6		22.7	22.1					
H. E. H.	October 27	20.0	21.2	20.9	21.1					

external evidence of cardiac or respiratory disease either observation. The general physical condition greatly on the two days of experimentation. Exercise was done at a time when he was physically fit. He had much sugar (28 grams in 24 hours) in his urine. The saturation of hemoglobin in his arterial blood was 95% as the result of work. In the second observation (16th) his health had improved and all symptoms had disappeared. Urine. Although the amount of work was less than in the first observation, the exertion was normal for a person with a slight increase in the exertion.

Anemia In considering the results in anemic patients it must be remembered that with blood of low oxygen capacity the effect of any error in analysis is exaggerated. The chance of gaining a false impression from a limited number of observations is therefore greater with anemic blood than with normal. Nevertheless it is surprising to find that there was, in every observation in anemic persons, a diminution of the saturation of hemoglobin of the arterial blood following exercise. This was slight in two patients but was marked in both observations of the third.

Auricular fibrillation Two observations were made on Tony G. During the first the patient's heart was fibrillating. He did moderately severe work for two minutes with no essential change in the oxygen saturation of hemoglobin in the arterial blood. Ten days later an equal amount of work was done when conditions were apparently similar except that as a result of quinidin therapy the patient's heart was regular. In the second observation there was a distinct fall in the saturation of hemoglobin.

Tuberculosis Santos C. had an extensive fibroid pulmonary tuberculosis involving the entire left lung and the upper lobe of the right. He also had a marked secondary anemia (12.5 volumes per cent oxygen capacity). While resting, the saturation was normal, within the limits of error, 93 per cent. After a moderate amount of exertion, the arterial saturation was only 84 per cent.

Emphysema None of the three subjects had any obvious circulatory difficulty at the time of the observations. William R. had a definite though not very severe type of emphysema. During rest the saturation of hemoglobin of arterial blood was normal, a condition which was not changed by a moderate amount of exercise. Joseph B. had a more obvious emphysema, but while resting had a normal saturation of hemoglobin. Following a smaller amount of work the saturation was diminished.

John L. was suffering from a more advanced degree of emphysema. At rest he was cyanotic. Dyspnea was apparent both in inspiration and in expiration. In three different samples taken at rest the saturation of hemoglobin in his arterial blood was approximately 80 per cent. With a small amount of exercise (only 1594 kilogram meters in $3\frac{1}{2}$ minutes), a remarkable result was obtained. The hemoglobin

saturation of the arterial blood fell from 78 per cent while resting to 23 per cent 1 to 2 minutes after exercise. The oxygen content of arterial blood fell from 17.5 to 5.2 volumes per cent. The resting arterial hemoglobin saturation in this patient was about that of normal mixed venous blood while the arterial saturation after exercise was far below any values previously reported.

Table 2 presents the results on normal individuals and is reproduced here for comparison. The saturation of hemoglobin increased in exercise. It is apparent that the patients reacted in a manner different from that of normal persons. Though only a few patients were studied and the variations in the saturation of hemoglobin before and after exercise were small, still it may be stated that in diseased subjects the saturation fell after exercise.

In attempting to throw light on the mechanisms involved in producing these changes it may be pointed out that in the tuberculous subject and in the patient with the advanced emphysema there must obviously have been difficulty in the diffusion of gases in the lungs which would lead to incomplete saturation of the hemoglobin of the blood in the lungs. In Harrop's patients (3) with polycythemia vera no abnormalities in the lungs were found on physical examination but he was able to determine a decreased permeability of the alveolar membrane to gases which he considered a probable cause for the diminished saturation of hemoglobin after exercise.

In the patient with cardiac decompensation many factors may have been instrumental in producing the final result. Pulmonary congestion and other factors might interfere with diffusion in the lungs thus diminishing the saturation of hemoglobin while a slower circulation rate might have the reverse effect (Lundsgaard (7), Blumgart and Weiss (8)). It seems possible that the decreased saturation of the hemoglobin with work, after quinidin therapy, may have been due to an increased circulation rate on the restoration of the normal rhythm of the heart. In the observation on the diabetic when severely ill and on the anemic patients, due to lack of evidence of definite changes in the lungs, the lowered saturation of hemoglobin is imputed to the same condition which causes a decreased saturation of hemoglobin on exhausting exertion of normal subjects, namely, an increase in the circulation rate when the volume of oxygen diffusing through

the pulmonary membrane has reached a maximum. The genesis of this condition was considered in the previous paper (1). It may suffice to say here that one of the factors causing increased diffusion of oxygen in the lungs is a decrease in oxygen tension of the venous blood and the latter must speedily come to its lower limit during exercise for even at rest the venous blood is quite unsaturated in severe anemia (Lundsgaard (9), Barr and Peters (10)).

An increased amount of oxygen in the inspired air might have raised the saturation of hemoglobin in the arterial blood of the patients during exercise and thus have produced a beneficial effect. Perhaps the situation here is similar to that observed by Briggs (11) who noted that the endurance of untrained man was increased on breathing oxygen while oxygen was of little aid to the trained athlete unless he carried exertion to the point of exhaustion. Perhaps in the untrained man, as in the sick subject, circulation rate is increased disproportionately to the volume of oxygen diffusing in the lungs.

SUMMARY AND CONCLUSIONS

1 Thirteen observations have been made during rest and after exertion on nine patients suffering from a variety of pathological conditions.

2 As a result of exercise, in eleven observations, there was a diminution in the degree of saturation of the hemoglobin in the arterial blood. In a patient with severe emphysema, the saturation fell from 78 per cent to 23 per cent with only slight exertion. In five of these eleven observations the oxygen content of arterial blood remained stationary or was diminished in spite of an increase in oxygen capacity.

3 These results are directly opposed to those upon normal individuals who, doing equal or greater amounts of work, have always shown an increased saturation of hemoglobin with oxygen and a higher arterial oxygen content, but are similar to those obtained with normal individuals doing much longer and more fatiguing amounts of work.

4 The experiments indicate that in ill and debilitated individuals during exertion the volume of oxygen diffusing through the pulmonary membrane is not enough to saturate the hemoglobin of the blood in the lungs. This suggests that the pulmonary mechanism may be a limiting factor in exercise—a factor which explains in part the inability of sick people to withstand exertion.

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CASE RECORDS

Case 1 William R. *Moderate diabetes* Age 29 years. Grocer's clerk. First noticed symptoms in July, 1922, when sugar was found in urine. Lost 40 pounds from July to October, 1922. On admission October 2nd his weight was 98 pounds. Urine examination showed sugar ++++, and a trace of diacetic acid. Except for emaciation physical examination was negative. Blood sugar on admission was 464 mg per cent. On October 30th, diet supposedly was carbohydrate 15 grams, protein 15 grams fat 90 grams, but the patient undoubtedly was breaking diet. Twenty four hour urine contained 280 grams of sugar. Reaction to exercise studied October 31st. On November 5th was transferred to metabolism ward where conditions were carefully controlled. Diet from November 5th to 10th, carbohydrate 15 grams, protein 15 grams fat 90 grams, sugar in

PROTOCOLS OF ANALYSES

		O ₂ content		O ₂ capacity		Remarks
		Before exercise	After exercise	Before exercise	After exercise	
William R	October 31, 1922 November 16, 1922	17 26	19 32	18 43	20 70	1764 k _g m in 3½ minutes Second blood 2-4 minutes after exercise
		17 62	18 96	18 16	21 60	
		19 13	21 22	20 63	21 44	2185 k _g m in 3½ minutes Second blood in 3 minutes after exercise
		19 49	21 13		21 47	
John O'R	July 26, 1923 August 2, 1923	14 70	15 10	15 61	17 19	2345 k _g m in 4 minutes Second blood 1 minute after exercise
		15 26	15 45	15 63	17 03	
		17 18	17 09	17 01	18 71	2400 k _g m in 3½ minutes Blood obtained 1-2 minutes after exercise
		17 38	16 23	16 92	17 63	
Antonia O	August 29, 1923	16 84	16 53			
		8 48	9 47	8 95	10 54	2796 k _g m in 15 minutes Second blood 1½-2½ minutes after exercise
		8 82	10 10	9 48	10 45	
		8 92	9 38	8 75		
Patrick M	July 31, 1923 August 7, 1923	5 91	5 54	5 92	6 47	1488 k _g m in 3½ minutes Second blood 1-1½ minutes after exercise
		6 37	5 53	6 38	6 38	
		5 89		6 47	6 10	
		5 60	4 70	5 35	5 87	1755 k _g m in 3½ minutes Second blood 1½-2½ minutes after exercise
Tony G	August 10, 1923 August 20, 1923	5 60	4 88	5 80	6 44	
				5 6	6 09	
		17 68	18 52	19 33	20 93	1410 k _g m in 2 minutes, patient stopped because of pain in all muscles Second blood complete in 2 minutes after exercise
		17 66	18 87	19 34	20 93	1575 k _g m in 2½ minutes
		17 79	18 24	18 46	21 08	
		17 79	18 43	18 57	21 32	

William Ru	{ July 19 1923	20 15	21 17	21 33	22 61	1804 kgm in 2½ minutes after exercise	Second blood 1-2 min-
		20 50	21 52	21 40	22 34		
Joseph B	{ August 8 1923	19 27	19 66	20 29	21 60	1155 kgm. in 3½ minutes	
		19 63	19 81	20 29	21 60		
		19 48					
John L.	{ August 9 1923	17 53	5 19	22 16	22 57	1596 kgm. in 3½ minutes after exercise	Second blood 1-2 min
		17 53	5 18	22 57			
Santos C	{ August 3 1923	12 85	12 71	12 85	14 64	2400 kgm in 3½ minutes	
		12 23	11 97	13 46	14 56		

24-hour specimen fell from 96.5 grams on November 6th to a trace on November 10th. Total acetone in urine fell from 8.8 grams on November 6th to 3.2 grams on November 10th.

Case 2 John O'R. Possible pernicious anemia Age 55 years Policeman. Six weeks before admission had noticed dizziness, weakness, dyspnea on exertion, indigestion (retching), and yellow color of face and loss of 20 pounds. Previously he had always been athletic. Admitted June 6, 1922. Physical examination revealed a well-developed man with pasty color of face and pale mucous membranes. Chest showed no abnormality. Arteries were slightly thickened. Test meal disclosed no free hydrochloric acid in stomach. X-ray examination of gastrointestinal tract was negative. Stools negative for blood, and Wassermann negative. Red blood cells 1,184,000. Hemoglobin 36 per cent at time of admission. On July 24th hemoglobin was 60 per cent. First reaction to exercise was studied on July 26th. On July 30th, hemoglobin was 75 per cent, and on August 2nd, second observation on exercise was made. At time of observation, weight was 69.4 kg and height 185 cm. West's factor, surface area in health $\times 2.5$, was used for calculating the vital capacity (see West, H. F., Arch. Int. Med., 1920, xxv, 306). Calculated vital capacity, 5250 cc. Observed vital capacity, 4800 cc.

Case 3 Antonia O. Banti's disease? Age 32 Native of Uruguay. History of excessive use of alcohol. Chief complaints were weakness and vomiting of blood which began one year ago. Since admission (June 6, 1923) had brought up coffee-grounds vomitus twice and passed both bright and dark colored blood in stools. Red blood cells 1,500,000. Hemoglobin (Tallquist) 20 per cent. Physical examination—mucous membranes pale, heart normal except for blowing systolic murmur. Blood pressure 92 mm mercury systolic, 44 mm mercury diastolic. Liver was two inches below costal margin, firm and not tender. On August 27th, 8 quarts ascitic fluid were removed from abdomen. On August 29th, exercised on bicycle ergometer. Weight 62.4 kg. Height 166 cm. Calculated vital capacity 4230 cc. Observed vital capacity 3200 cc.

Case 4 Patrick M. Pernicious anemia Age 62 Born in Ireland. Gradual onset of dyspnea on exertion, weakness, loss of appetite. At time of observation there was intermittent epigastric pain, insomnia and nocturia three to five times. Best weight 184 pounds. Physical examination—pale yellow skin, short thickset man with prognathous jaw. Chest well developed. Heart negative except for short blowing systolic murmur not transmitted. Pulse rate varied from 70 to 90 per minute. X-ray of chest was negative. Blood picture, June 5th, red blood cells, 2,400,000. Hemoglobin (Tallquist) 35 per cent. White blood cells 8,500. Blood pressure 110 mm systolic, 80 mm diastolic. Reaction to exercise studied July 31st and August 7th. Weight, 71.6 kg. Height, 166 cm. Calculated vital capacity, 4500 cc. Observed vital capacity, 3400 cc.

Case 5 Tony G Auricular fibrillation Spaniard, age 30 On April 7th was admitted into hospital with lobar pneumonia. Left hospital cured in eighteen days After working for two weeks noticed that his heart was very rapid and was forced to stop work because of pain down left arm On readmission June 18th, heart was regular at 150 beats per minute, and generally enlarged with point of maximum impulse in sixth intercostal space Electrocardiogram disclosed no abnormality except tachycardia On July 9th heart became completely irregular Patient was readmitted August 2nd with a wholly irregular heart and a pulse deficit Reaction to exercise studied August 10th. August 18th quinidin therapy was started On August 19th had palpitation for two hours following which there was sudden return to regular rhythm of the heart at rate of 100 The patient had received 2.4 grams of quinidin by August 20th and his pulse was regular at 69 beats per minute. Reaction to exercise was studied on this day Weight 86.7 kg Height 160 cm Calculated vital capacity, 4750 cc Observed vital capacity before and after quinidin 3500 cc.

Case 6 Santos C Chronic pulmonary tuberculosis Age 28 Two years ago began coughing and glands in left axilla became swollen On operation they were found to be tuberculous Three months later glands in neck became swollen Two months ago there began hemoptysis, night sweats, pain over left chest, dyspnea on exertion Was admitted to hospital June 18th with enlarged glands in left axilla and neck and discharging sinuses At this time afebrile pulse rate varied between 80 and 88 beats per minute Physical and x ray examinations revealed fibrosis and infiltration throughout entire left lung and fibrosis of right upper lobe Blood picture red blood cells 4,240,000, hemoglobin 65 per cent. Weight 69.0 kg Height 181.5 cm Calculated vital capacity, 4750 cc Observed vital capacity, 3200 cc.

Case 7 William Ru Angina pectoris, mild diabetes and emphysema of four years duration Age 53 Entered hospital July 13th, 1923, because of anginal attack of one week's duration, with pain radiating down left arm While in hospital, routine examination of urine disclosed diabetes of mild degree. Sugar ++, no acetone, nor diacetic acid in urine Sugar in blood 200 mg Carbon dioxide combining power of plasma 45 volumes per cent. Both the angina and the evidences of diabetes rapidly subsided. The patient's reaction to exercise was studied July 19, 1923 On physical examination the patient was slightly dyspneic and orthopneic The chest was large and barrel shaped, hyperresonant to percussion The breath sounds were obscured by long musical murmurs and expiration was difficult and prolonged Fluoroscopic examination showed a normal arch and a heart enlarged to right and left. The lungs were negative and the costophrenic sinus was clear Weight 76 kg Height 169.5 cm Calculated vital capacity 4680 cc. Observed vital capacity 2900 cc

Case 8 Joseph B *Emphysema* Age 43 Emphysema(?) starting at age of 23 Asthmatic attacks for five years, better in summer, worse in winter, caught cold easily and was sensitive to chicken feathers Patient was short and obese with cyanosed face, hands and feet, and an expiratory dyspnea Chest was large, hyperresonant with sibilant and sonorous rhonchi Vocal fremitus was transmitted to surface of chest Sputum contained eosinophiles and no acid-fast bacilli X-ray of chest showed sclerosis of aortic arch and heart enlargement to left, emphysema, no tuberculosis Weight 86.7 kg, Height 160 cm Calculated vital capacity, 5220 cc Observed vital capacity, 1700 cc

Case 9 John L *Emphysema* Age 49 For last 13 years there was increasing dyspnea especially on exertion and a loss of 32 pounds in weight Patient was a heavy drinker and smoker Physical examination disclosed marked cyanosis of lips and fingers, orthopnea and dyspnea which was both expiratory and inspiratory Accessory muscles of respiration were used but chest expansion was very poor and chest wall was rigid The chest was hyperresonant Vocal fremitus and voice sounds were transmitted to surface of chest and breath sounds were poorly heard There were a few dry râles over chest Heart, left border fifth intercostal space, 9.5 cm from midsternal line Sounds of fair quality and regular Fluoroscopic and x-ray examination—lungs emphysematous, thorax elevated as one piece, intercostal spaces wide, diaphragm descended slightly on both sides (marked limitation) No evidence of fluid or adhesions or masses in mediastinum Aorta and heart were normal Increased fibrous tissue production in bronchial wall Diagnosis—chronic bronchitis, emphysema Weight 71.8 kg Height 183 cm Calculated vital capacity, 5220 cc Observed vital capacity, 3100 cc

THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART IN NORMAL MAN

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INTRODUCTION

There is a general agreement of opinion that digitalis increases the output of the heart per unit of time. This opinion is based in large part upon pharmacological experiments upon animals. Although in some of these experiments, as Cohn (1915) has pointed out, the dose was greater than that administered to patients there is little doubt that in animals which have been subjected to operative procedures the output of the heart is increased by digitalis. The careful studies of Wiggers (1927), to which further reference will be made, have recently added support to this generally held opinion.

It is also generally considered that the familiar manifestations of heart failure are brought about by a reduction in the output of the heart per minute. Because of this conception of heart failure and because of the favorable results following the administration of digitalis to patients with heart failure, it has been assumed by many observers that digitalis increases the output of the heart in patients. Nevertheless Harrison and Leonard (1926) observed a diminution in the output of the intact dog's heart after the administration of digitalis in doses calculated to be of the same order as those given to patients. This diminution occurred in all the dogs studied, both narcotized and non-narcotized. This reversal of previous findings has such significance, not only as regards the conception of digitalis action but also as applied to existing theories of cardiac failure, that a study of the effect of digitalis upon the output of the human heart seemed worth while.

Direct measurements of the output of the human heart before and after the administration of digitalis have been made only by Eppinger, von Papp and Schwartz (1924). Their single subject, who was suffering

from heart failure, showed a fall in cardiac output during a period of clinical improvement which followed the administration of digitalis. For reasons which will presently be discussed, however, it is believed that measurements of the cardiac output by existing methods in persons with congestive heart failure are to be looked upon with scepti-

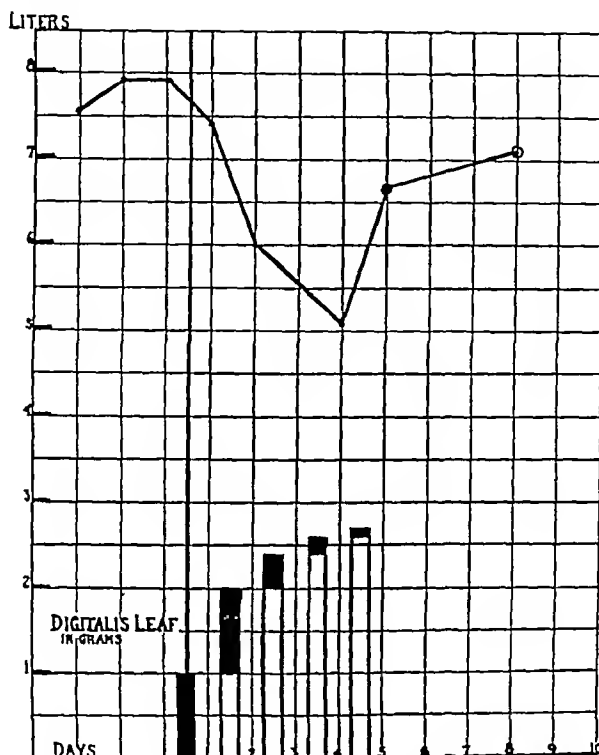


FIG 1 CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 1

In this and in subsequent figures the points surrounded by circles indicate determinations made during periods of nausea

cism Cohn and Stewart (1924) studied the effect of digitalis in patients by means of a moving x-ray film. They observed an increase in the amplitude of the left ventricular excursion after digitalis in 4 subjects suffering from heart disease. No other observations seem to bear directly on the problem of the effect of the drug on the cardiac out-put of man

METHODS

The output of the heart was observed before and after the administration of digitalis leaf of known potency in a series of normal men. During the studies, observations were also made of changes in "basal" pulse rate and other changes were recorded. The output of the heart was measured by the method of Field, Bock, Gildea and Lathrop (1924), a method which requires no punctures of blood vessels and therefore lends itself to repeated application to the same subject. It involves the determination by respiratory methods of the carbon dioxide tension in the blood entering and leaving the lungs and the measurement of the total gas exchange by the gasometer method. During the necessary procedures, 8 to 12 half minute counts of the pulse rate were made, the average of these counts is designated the "basal pulse rate."

TABLE 1
The effect of digitalis upon the output of the heart of subject 1

Date	Conditions	A-V difference	CO ₂ per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	R.M.R.	Remarks
October 15	Normal	2 29	173	7,550	64	118	0 78	-7	
October 26	Normal	2 42	191	7,900	69	115	0 81	-5	
October 27	Normal	2 24	177	7 900	67	118	0 80	-10	
October 29	Digitalis 1 0 gram	2 20	163	7,400	62	119	0 78	-16	
October 30	Digitalis 2 0 grams	2 90	174	6,000	59	102	0 79	-11	
November 1	Digitalis 2 6 grams	3 37	171	5,080	57	88	0 75	-9	
November 2	Digitalis 2 7 grams	2 82	189	6,700	61	110	0 75	±0	Toxic
November 5		2 42	172	7,100	60	119	0 75	-8	Toxic
November 8		2 55	182	7,140	60	119	0 81	-10	Toxic

Care was exercised to maintain the conditions of the experiment as uniform as possible from day to day. All observations were made in the morning with the subject in the post-absorptive condition. The subject rested in a reclining position in a wheel chair for 30 to 45 minutes before the experiment, his position in the chair was not changed during an experiment or from day to day. Fluctuations of room temperature were kept at a minimum.

The usual procedure was to train the subject in the necessary respiratory measures on one or two occasions before his cardiac output was actually determined. The control observations were made on successive days until an apparently normal level was established. If, as was sometimes the case, the first one or two experiments gave higher values than subsequent ones these high figures were discarded.

Digitalis leaves were given by mouth. The initial dose was usually one gram, and this was followed by smaller daily doses (0.2 to 0.8 gram) until a stage of undoubted digitalis effect was reached, as judged by changes in the pulse rate and the electrocardiogram, and by the occurrence of nausea. Observations of cardiac output and of basal pulse rate were made daily during the periods of administration and of maximum effect and at slightly longer intervals during the recovery period.

Five such experiments were carried out upon four individuals. In the case of the individual who was studied twice a period of two months elapsed between the last dose of digitalis in the first study and the beginning of the second.

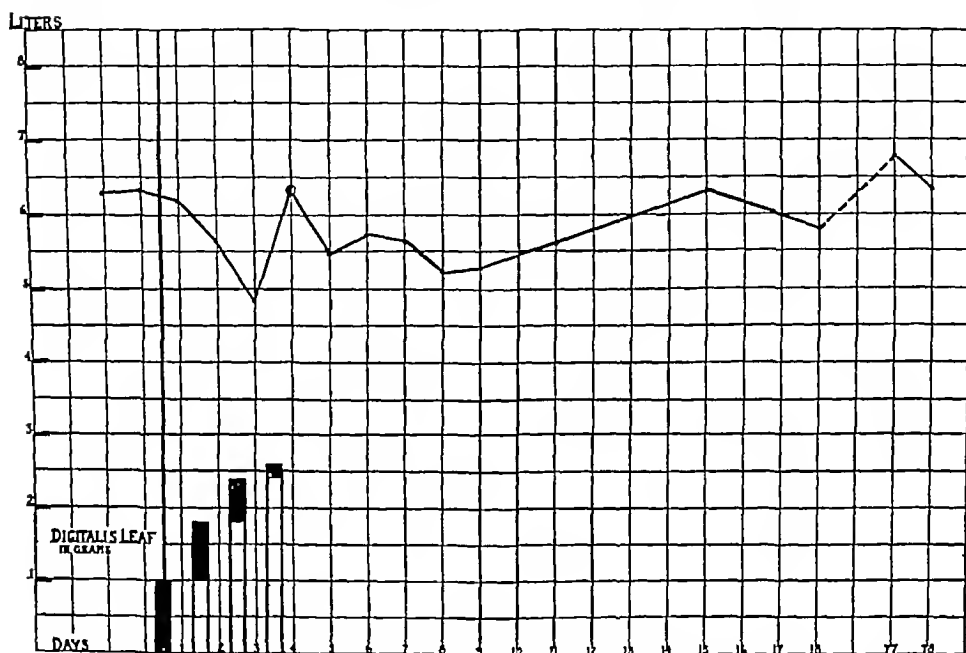


FIG. 2. CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 2

RESULTS

The observations on the output of the heart are summarized in Tables 1 to 5, and represented graphically in figures 1 to 5.

The tables also record the observations upon the difference in the carbon dioxide contents of venous and arterial blood (A-V difference), the excretion of carbon dioxide per minute (CO_2 per minute), the output of the heart per minute, the pulse rate, the output of the heart per beat, the external respiratory quotient (R.Q.), and the basal metabolic rate (B.M.R.).

The output of the heart

Analysis of the tables and figures indicates that the care given to maintaining nearly identical conditions in successive experiments succeeded in its object, as the subjects had relatively stable outputs during the control observations. Following the administration of the first gram of digitalis leaf there was usually no definite change. The ingestion of the second gram was in each case followed by a slight diminution in the output of the heart and succeeding doses were followed by a further reduction.

TABLE 2
The effect of digitalis upon the output of the heart of subject 2

Date	Conditions	A-V difference	CO ₂ per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.	Remarks
			cc	cc					
November 15	Normal	3.07	193	6,280	59	106	0.79	-11	
November 16	Normal	3.13	196	6,300	58	109	0.78	-5	
November 17	Digitalis 1.0 gram	3.19	197	6,180	57	108	0.80	-7	
November 18	Digitalis 1.8 grams	3.32	187	5,640	53	107	0.73	-8	
November 19	Digitalis 2.4 grams	3.86	186	4,820	50	96	0.79	-14	Toxic
November 20	Digitalis 2.6 grams	3.07	194	6,320	53	119	0.79	-10	Toxic
November 21		3.44	188	5,460	53	103	0.75	-9	Toxic
November 22		3.23	185	5,720	51	112	0.82	-16	Toxic
November 23		3.44	194	5,640	53	107	0.84	-15	Toxic
November 24		3.70	198	5,220	52	100	0.87	-16	
November 26		3.61	190	5,260	53	100	0.82	-15	
November 28		3.36	188	5,600	56	100	0.84	-17	
December 1		3.02	190	6,300	57	110	0.80	-13	
December 4		3.15	183	5,800	55	105	0.79	-15	

With the occurrence of nausea, however, in each case the output of the heart increased toward the pre-digitalis level, and in one instance (fig. 3) actually exceeded that level. With the onset of nausea the administration of the drug was discontinued. The first subject (table 1, fig. 1) was studied only up to this point, i.e., the occurrence of nausea and the return of the cardiac output toward the pre-digitalis level. The other subjects were observed throughout the period of

nausea and the later period of diminishing digitalis effect. These subjects during the period of nausea continued to have a cardiac output little if any below their usual levels. With the subsidence of the nausea, however, there occurred in 3 instances out of 4 a second period of diminished cardiac output, in which the reduction was comparable to that observed during the initial digitalis effect. The other subject (fig 5) received a smaller dose than the others and had slight nausea

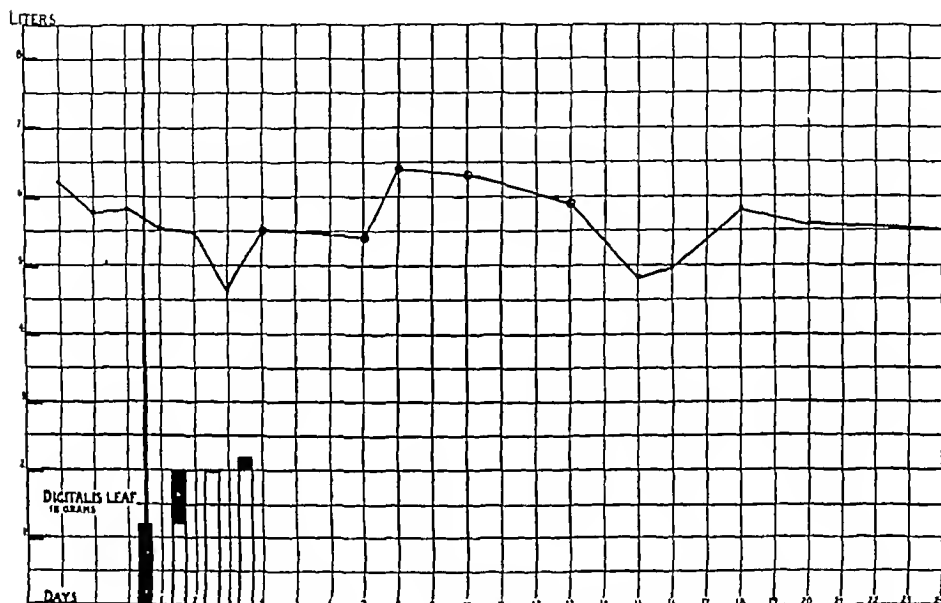


FIG 3 CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 3

for only a few hours. In his curve the rise usually associated with nausea is not present.

Following this secondary drop the curve in each case returned to the pre-digitalis level or slightly below it. The return to the zone of cardiac output usual for the individual occurred in from 11 to 14 days after the cessation of digitalis administration.

Table 6 and figure 6 represent the results of an arbitrary division of our experiments into 5 periods or phases, as follows

- 1 Before digitalis
- 2 Between the first dose and the onset of nausea

- 3 The duration of nausea
- 4 Between the termination of nausea and complete recovery
- 5 Recovery

The division was suggested by the occurrence of phases in the curves corresponding to these periods. This grouping of results serves to emphasize the change already noted and to permit the calculation of the average change in cardiac output produced by digitalis. Figure 6 shows the average results: the average fall during the period of admin-

TABLE 3
The effect of digitalis upon the output of the heart of subject 3

Date	Conditions	A-V difference	CO per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	R.M.R.	Remarks
		"	"						
December 14		3 13	194	6 200	60	103	0 79	-14	
December 15		3 36	193	5 740	58	100	0 79	-14	
January 11		3 12	181	5,600	55	105	0 76	-17	
January 12	Digitalis 1 2 grams	3 31	183	5 530	54	102	0 79	-19	
January 13	Digitalis 2 0 grams	3 36	184	5,490	50	110	0 78	-18	
January 14	Digitalis 2 0 grams	3 86	179	4,630	51	91	0 78	-20	
January 15	Digitalis 2 2 grams	3 36	186	5 500	49	112	0 80	-18	Toxic
January 18		3 44	185	5 400	51	106	0 73	-14	Toxic
January 19		2 90	186	6,400	50	128	0 72	-11	Toxic
January 21		3 04	191	6 300	49	128	0 80	-17	Toxic
January 24		3 04	179	5 900	49	120	0 79	-20	Toxic
January 26		3 77	182	4,830	47	103	0 77	-18	
January 27		3 77	187	4 950	52	95	0 74	-13	
January 29		3 22	186	5 790	50	116	0 77	-16	
January 31		3 40	189	5,560	46	121	0 83	-20	
February 4		3 27	180	5,500	55	100	0 75	-17	

istration was to 84 per cent of the normal level. During the period of nausea the cardiac output was 94 per cent of the volume before digitalis, but with the subsidence of nausea it fell to 82 per cent, to return ultimately to 96 per cent of the previous level. That the output of the heart remained, even after the lapse of weeks, somewhat below the pre-digitalis level, may be ascribed to greater coöperation and less effort on the part of the subject.

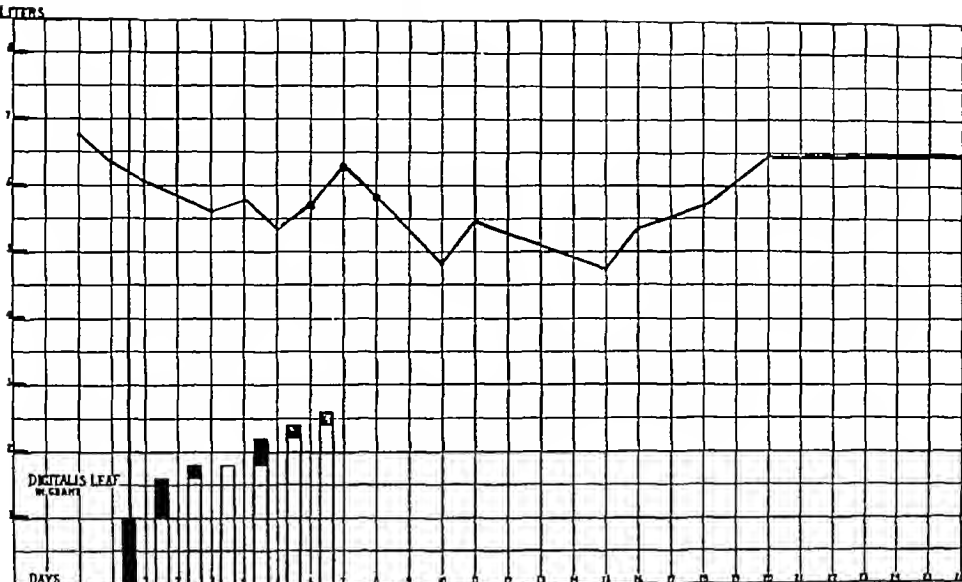


FIG 4 CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 2 (TWO MONTHS AFTER HE RECEIVED DIGITALIS PREVIOUSLY)



FIG 5 CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 4

TABLE 4
The effect of digitalis upon the output of the heart of subject 4 (two months after he received digitalis previously)

Date	Conditions	A \ difference	CO ₂ per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.	Remarks
February 19	Normal	2 90	196	6,760	61	110	0 82	-12	
February 20	Normal	3 15	199	6,320	61	104	0 81	-11	
February 21	Digitalis 1 0 gram	3 28	190	5,800	55	105	0 80	-12	
February 23	Digitalis 1 8 grams	3 36	188	5,600	54	104	0 80	-14	
February 24	Digitalis 1 8 grams	3 32	192	5 790	55	105	0 79	-11	
February 25	Digitalis 2 2 grams	3 70	197	5,320	54	99	0 83	-13	
February 26	Digitalis 2 4 grams	3 44	197	5,700	54	105	0 81	-11	
February 27	Digitalis 2 6 grams	3 15	198	6 290	54	117	0 81	-11	Toxic
February 28		3 36	196	5,820	54	108	0 81	-11	Toxic
March 2		3 82	183	4 800	52	92	0 77	-14	Toxic
March 3		3 40	185	5,440	54	100	0 79	-14	
March 7		3 82	181	4 740	54	88	0 75	-13	
March 8		3 65	196	5 360	53	102	0 79	-10	
March 10		3 32	189	5 700	53	108	0 79	-13	
March 12		3 02	195	6,460	56	115	0 77	-8	
March 18		2 90	188	6 480	58	112	0 77	-11	

TABLE 5
The effect of digitalis upon the output of the heart of subject 4

Date	Condition	A \ difference	CO ₂ per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.
March 15	Normal	2 86	208	7 290	68	107	0 80	+5
March 16	Normal	2 65	201	7,560	73	103	0 78	+3
March 25	Digitalis 1 0 gram	3 50	201	5,740	58	99	0 86	-5
March 26	Digitalis 1 4 grams	3 02	193	6 400	62	103	0 84	-6
March 27		3 44	203	5 900	59	100	0 86	-3
March 28		3 19	201	6 300	55	115	0 86	-4
March 29		3 32	198	5,960	57	105	0 86	-6
April 2		3 06	196	6 400	58	110	0 81	-1
April 4		3 36	201	6 000	64	94	0 81	±0
April 6		2 98	198	6 650	60	111	0 83	-3
April 9		3 11	205	6 600	62	106	0 81	+2
April 12		3 07	200	6,520	63	103	0 84	-3
April 15		3 36	207	6 200	68	91	0 82	+2
April 19		2 98	192	6 450	67	96	0 78	-1
April 23		2 94	192	6 630	63	104	0 80	-2

The pulse rate

In each of the five experiments there occurred a definite drop in the basal pulse rate. The difference between the average pulse rate during the control experiments and those during the initial digitalis

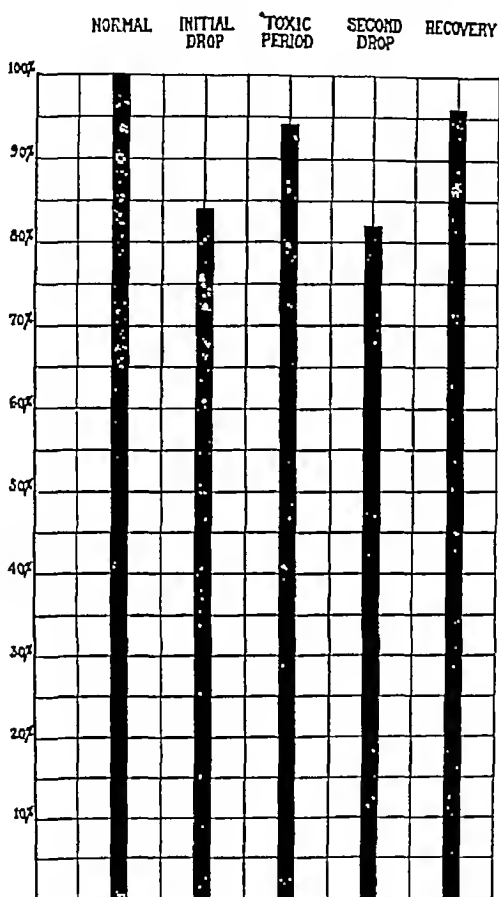


FIG 6 THE PERCENTAGE CHANGE IN CARDIAC OUTPUT DURING SUCCESSIVE PHASES OF DIGITALIS EFFECT

effect varied from 5 to 12 and averaged 7 beats per minute. The onset of nausea was associated with an acceleration of only 1 or 2 beats per minute, and its subsidence with a fall to the lowest level observed in each case. Figure 7 is a graphic portrayal of the average pulse rates

[illegible][illegible]

before digitalis and during successive weeks after its administration. It will be seen that there is in each case a fall and then a gradual return to the normal level, which is usually reached in the fourth week. The effect on the pulse rate thus outlasts the effect on the cardiac output.

The output of the heart per beat

The diminution in the output of the heart per minute is relatively greater than the fall in pulse rate. Hence there must be a diminution in the systolic output, that is to say, the output per beat, as may be seen in tables 1 to 6. The period of nausea with increase in output

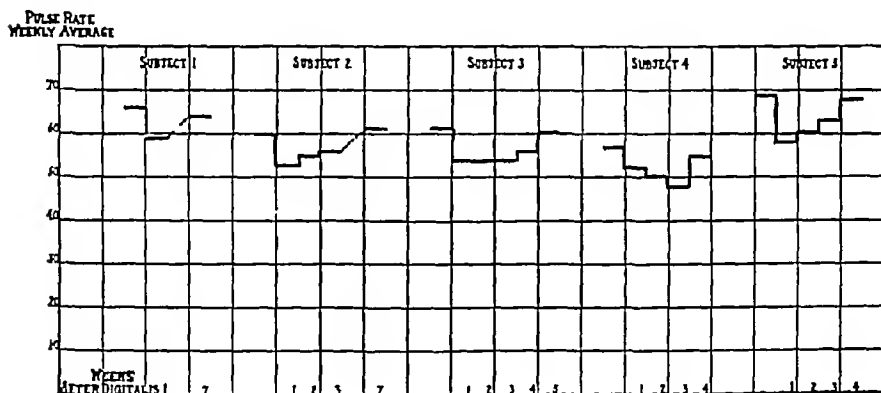


FIG. 7 THE EFFECT OF DIGITALIS ON THE BASAL PULSE RATE

per minute toward the normal level and the continued slow pulse was sometimes associated with an output per beat in excess of the one usual for the individual. The secondary drop in cardiac output, however, was accompanied by a corresponding fall in the volume expelled by the heart per beat.

The electrocardiogram

The galvanometric tracings showed in each case a flattening of T-waves in all leads. In one case T_s became diphaseic. Sinus arrhythmia became more marked. The P-R interval was not prolonged more than 0.02 second in any tracing.

Subjective effects

Each individual experienced nausea, lasting in different instances from 1 to 10 days. None vomited, all suffered a greater or less degree of anorexia. All complained of a curious and indescribable depression of spirits and activity, which outlasted the nausea. None had diarrhea.

Blood pressure

No consistent changes in either systolic or diastolic blood pressure were observed.

Basal metabolic rate

As is usually the case when trained subjects are studied the basal metabolic rates were uniformly low. In several cases the lowest rates observed were obtained during the period of maximum digitalis effect but the changes were too slight to have significance.

DISCUSSION

The output of the heart per minute under ordinary conditions of life is a constantly changing value. It changes with position, with temperature, and it changes tremendously with increased oxygen consumption during exercise. It is therefore somewhat surprising that digitalis, which affects cardiac activity both by direct myocardial action and through the nervous system, should produce such relatively small changes in the output per minute. Certainly if the drug may produce an increase in the output of the normal heart one might expect unmistakable evidence of it in such experiments as these. Such an increase was not, however, observed, on the contrary there was in each case a definite decrease, and that decrease was observed in a group of subjects whose cardiac output was already as low as rest, fasting, and training could bring it. The decrease was not large but strikingly consistent when the normal variation in cardiac output and the possibilities of technical error are considered.

It is difficult to reconcile these observations and those of Harrison and Leonard with the cardiodynamic studies of Wiggers. This in-

vestigator, using optical methods of registration, studied the effect of digitalis upon the intraventricular pressure curves under carefully controlled conditions. He concludes that digitalis acts as a cardiac stimulant, that is, it improves the contractile force of the ventricular beat and increases the systolic discharge. The possibility must be considered, however, that even the same pharmacological effect upon cardiac muscle might produce a different effect upon the output of the heart of an animal which has been subjected to severe operative procedures and upon the output of the heart of a normal human subject. If the same pharmacological effect upon heart muscle can produce different effects upon cardiac output in different states of heart muscle, it is then unsafe to apply our conclusions directly to an analysis of the effect of digitalis upon the cardiac output of patients suffering from heart failure. For example, a drug which by increasing the tonus of heart muscle diminishes the output per beat of a normal heart might by an exactly similar action on the muscle increase the output per beat of a dilated and insufficient heart. Therefore, until some method for the determination of cardiac output has been shown to be trustworthy in patients with heart failure the most important application of this concept of digitalis action must be made, if made at all, upon the basis of indirect evidence.

The experiments of Cohn and Stewart (1924) present indirect evidence that the output of the heart is increased by digitalis, as their x-ray observations demonstrate an increased amplitude of the ventricular excursions following the administration of digitalis. Since there was no measurable diminution in the total size of the hearts studied this is evidence of increased output although the changes are very small. Their subjects, however, were patients with heart disease, and that introduces complications which make their experiments not comparable with ours.

Reliable current methods such as those devised by Plesch (1909), Krogh and Lindhard (1912), Douglas and Haldane (1922), Field, Bock, Gildea and Lathrop (1924), Burwell and Robinson (1924), all depend upon equilibrium between a gas or gases in the alveolar air and those in the pulmonary capillaries. Under the conditions imposed by pulmonary congestion such an equilibrium may be impossible to attain (Peters and Barr (1921)).

Blumgart (1927) has studied the *velocity* of blood flow before and after the administration of digitalis to normal men, and finds that there is no substantial change. This observation, whether compared with the concept of digitalis as increasing or as decreasing cardiac output, suggests that velocity and volume do not necessarily vary together. They need not vary together of course if there is a coincident change in the volume of the circulatory fluid. Such changes in volume might be brought about by the effect of digitalis upon the vessels, an effect which Gottlieb (1924) and others believe to be of great importance.

The significance of the change in cardiac output associated with nausea is not known. During the period of nausea three subjects had also a slight average increase in the basal metabolic rate. Both changes may be associated with the discomfort of the sensation.

SUMMARY

In a small series of normal men the administration of from 1.4 to 2.7 grams of digitalis leaf was followed by a diminution in the output of the heart per minute and per beat, and in the basal pulse rate. This diminution was comparable to that found by Harrison and Leonard (1926) after the administration of digitalis to normal dogs.

When nausea was produced by digitalis there was a tendency for the cardiac output per minute to return toward the normal level. The pulse rate remained slow at this time so that the output per beat often increased to above the amount usual for the individual. The subsidence of nausea was accompanied by a second period of diminished cardiac output.

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A STUDY OF EXPERIMENTAL ANEMIA IN DOGS THE ACTION OF BEEF LIVER AND IRON SALTS ON HEMOGLOBIN REGENERATION

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Recent contributions to the study of hemoglobin regeneration in secondary anemia have laid stress on the therapeutic value of natural food products (1) (2). These reports have led to the indiscriminate administration of glandular organs, notably liver, to patients who had some form of secondary anemia.

The present investigation was undertaken in order to determine the exact rôle of iron salts in hemoglobin formation in long standing experimental anemia, and to study the effect of feeding beef liver on hematopoietic activity. The exhaustive and well-controlled experiments of Whipple and his associates have advanced our knowledge greatly. However, the use of a wide variety of food products and the attempts to control the metabolism of pigment, and blood cell stroma, have introduced an element of uncertainty with regard to the quantitative effect of iron in bone marrow activity.

In experimental work of this type the factor of relative depletion of the body iron reserve cannot be over-emphasized. An adequate vitamin intake must be assured in order to maintain a healthy bone marrow (3). In the matter of iron depletion, years of clinical observation have demonstrated that in prolonged hemorrhage, from whatever cause, the administration of some form of iron is directly beneficial, without necessarily having a specific stimulating effect upon the bone marrow itself. Whipple and Robschert-Robbins (2) have stated that the feeding of liver had a well-marked effect upon hemoglobin regeneration. In attempting to confirm this observation it seemed plausible to substitute for glandular organs an adequate supply of vitamin in the diet, and to study the effect of adding and withholding iron salts.

The general plan of study followed the methods of Whipple and Robscheit-Robbins, but several modifications will be described. Dogs were fed the basal bread mixture (C) (4), substituting for the salt mixture 500 cc of whole milk to the daily ration. This insured the presence of an adequate amount of vitamin B. Facilities were not available to determine the iron content of the diet, but it was probably quite low. Preliminary experiments were carried out by feeding the original bread mixture of young rats previously deprived of vitamin B. When the bread was fed, the resulting growth curves showed a definite lag in the weights of the animals, as compared with the controls. The addition of milk had a further advantage for the animals consumed the bread mixture completely.

Plasma volume estimations were omitted, because the dogs were bled at intervals of at least two days, this is considered ample time for readjustment of the blood volume following moderate hemorrhage. The amount of blood withdrawn each time depended upon the hemoglobin percentage found at the time of the previous bleeding. After some experience, the size of the hemorrhage necessary to keep the hemoglobin level at about 50 per cent could be estimated. The amount of blood withdrawn varied from 30 cc to 300 cc. The small samples of blood taken between the larger bleedings were helpful in determining the rate of hemoglobin regeneration and in deciding upon extent of the succeeding hemorrhage. As the protocols show, the larger hemorrhages were produced at fairly long intervals.

Hemoglobin determinations were made by the oxygen capacity method of Van Slyke and Stadie, the value of 18.5 volumes per cent being used as a standard, with 13.8 grams of hemoglobin per 100 cc of blood. Red blood cell counts and reticulated cell counts were made by standard methods when indicated. Blood was drawn under oil from the femoral arteries, without exposing the vessel and without stasis, dry potassium oxalate being used in just sufficient quantity to prevent coagulation (0.2 per cent).

The periods of experimental feeding were usually ten days in duration when liver, thymus, and commercial nucleic acid were used. An observation period of twenty days was usually allowed in which to note the latent effect of the food upon hemoglobin regeneration. Iron was administered usually in the form of ferric citrate in amounts

of 0.8 gram daily, dissolved in water and mixed with the diet. This amount was chosen in order to provide a definite excess of the mineral without producing toxic symptoms. In two experiments ferrous carbonate was used. In contrast to the method of feeding liver, the administration of iron salts was continuous throughout the experimental period.

The experiments were planned to show the effect on hemoglobin regeneration of (1) adequate iron intake in combination with liver, (2) liver feeding in the presence of iron depletion, and (3) the effect of iron salts alone.

TABLE 1
Rate of hemoglobin regeneration when iron was added to the basal bread mixture

Dog number	Days	Added to diet	Average weight of dog	Hemoglobin regenerated		
				Total grams	Grams per day	Grams per kilogram of animal per day
8	38	Ferric citrate	13.63	84.0	2.21	0.162
3	40	Ferric citrate	12.72	68.8	1.72	0.135
69	35	Ferric citrate	15.23	82.5	2.357	0.155
72	25	FeCO ₃ —0.6 gram	15.05	47.0	1.88	0.121
4	47	Ferric citrate	12.8	101.0	2.149	0.175
70	37	Ferric citrate	14.4	81.9	2.213	0.153
9	26	Ferric citrate	11.8	48.0	1.843	0.156

RESULTS

Table 1 shows the results observed when ferric citrate was added to the basal bread mixture. In these experiments the animals had previously been bled over a long period of time while being fed the basal diet, and relative iron depletion was present at the beginning of the experiments.

Table 2 shows the effect of adding 400 grams of raw beef liver to the diet each day for ten days. A period of twenty days was found to be sufficient for the effect of liver feeding to manifest itself, and this period was added to the feeding period (except in one case), making the total time for the experiment thirty days.

When liver was fed, a relation was apparent between the available

body iron (or relative iron depletion), and the rate of regeneration of hemoglobin. Referring to table 1, it will be seen in the experiment with dog 4, that when ferric citrate was used alone, the rate of regeneration of hemoglobin was 2 149 grams per day. While ferric citrate was being continued, the dog was fed 4,000 grams of raw beef liver during a period of ten days, and hemoglobin was recovered at the rate of 2 213 grams per day (table 2). No specific stimulation is apparent. In the experiment with dog 69, (table 2), 400 grams of liver per day were fed, beginning twelve days after the preliminary bleedings had started. This allowed little time for the depletion of the body iron reserve. When liver was added to the diet, the amount of hemoglobin recovered was 2 533 grams per day, and in a later

TABLE 2
Rate of hemoglobin regeneration when raw beef liver was added to the diet

Dog number	Days	Added to diet	Average weight of dog	Hemoglobin regenerated		
				Total grams	Grams per day	Grams per kilogram of animal per day
			<i>kgm</i>			
69	30	400 grams 10 days	13 2	76 0	2 533	0 1919
4	30	400 grams 10 days	13 0	66 4	2 213	0 1702
3	18	400 grams 10 days	11 7	24 5	1 36	0 1152
70	30	400 grams 10 days	14 4	48 3	1 61	0 1118
9	30	400 grams 10 days	11 8	47 8	1 593	0 135

experiment with iron alone, 2 351 grams per day was recovered. In the three experiments in table 2 in which relative iron depletion did precede the administration of liver (dogs 3, 70, and 9), the resulting regeneration of hemoglobin was somewhat greater than with the basal diet mixture alone, but *definitely less* than when iron was abundantly provided. In an animal given a series of rapid preliminary bleedings to reduce the hemoglobin level to 50 per cent, the rate of regeneration *immediately* following is greater than that caused by either liver feeding or iron administration. This is shown by an experiment with dog 8, in which the regeneration rate was 3 434 grams per day in a three weeks period, which had begun two weeks after the initial hemorrhage. (See protocol.) These observations illus-

trate the profound effect of the condition of the body iron reserve on experiments of this nature. Thus, when the iron reserve was high the hemoglobin regeneration was quite pronounced, both on the basal diet and when liver was added, but when the iron reserve was low, the hemoglobin regeneration could be increased to maximum by supplying iron salts alone.

Experiments were made to determine the efficacy of chlorophyll, wheat germ oil, and commercial yeast nucleic acid. The nucleic acid

TABLE 3

Dog number	Grams of hemoglobin regenerated per kilogram of dog per day		
	Nucleic acid added to diet	Raw thymus gland added to diet	Raw liver added to diet
	grams	grams	grams
3	0.250	0.2041	0.1152
69	0.125		0.1919
4	0.258		0.1702
70	0.1846		0.1118
2		0.2460	

TABLE 4

The effect of the bread and milk mixture alone on the rate of hemoglobin regeneration

Dog number	Days	Average weight of dog	Hemoglobin regenerated		
			Total grams hemoglobin	Grams per day	Grams per kilogram per day
3	30	12.6	41.6	1.386	0.11
72	28	14.5	38.3	1.367	0.094
4	32	12.3	28.0	0.875	0.071
9	25	12.36	27.5	1.10	0.089

was fed in moderate amounts (15 to 20 grams per day) for periods of ten days, and in calculating its effect a "carry-over" period of twenty days was allowed. The results are about equal to those derived from liver and the feeding of thymus gland, but only when iron was constantly supplied in the diet was the regeneration of hemoglobin increased. Table 3 shows these in comparison.

In table 4 are shown the results of feeding the basal bread mixture alone to dogs in which there was relative iron depletion. The diet

was not entirely iron free, and we have available only indirect data to show the amount of iron depletion in the animal's body. It is obvious, however, that the rate of hemoglobin regeneration is greatly depressed, when these results are compared with those in the preceding tables.

COMMENT

There was no evidence in these experiments to show that the feeding of beef liver is of especial value in anemia of long duration produced in healthy animals by hemorrhage. The conclusions to be drawn appear directly opposed to those of Whipple and Robscheit-Robbins, whose work this study has attempted to confirm. However, a fairly complete agreement may be secured in the conclusions by applying a different interpretation to the results of Whipple and Robscheit-Robbins. The latter investigators have appreciated the action of iron in experiments of this type, but apparently in their experiments there was not provided an adequate amount of iron in the animals' diets to control this factor and prevent possible iron depletion while administering natural food products. In drawing conclusions with regard to hemoglobin regeneration it seems that the body iron reserve must be fully protected if the effects of the iron content of the foods themselves are to be avoided.

According to Wells (5) the average human body contains about 3.2 grams of iron, of which 2.4 to 2.7 grams are in the blood. If we consider that the weight of a dog is one-sixth that of a man, then the iron content of the dog's body would be about 0.6 to 0.7 gram. In order to prevent the normal rebound of blood regeneration after hemorrhage, as described by Drinker (6), a very large amount of hemoglobin must be removed. An idea of the extent of the hemorrhage necessary to accomplish this may be obtained by a study of the protocols of dogs 8 and 72. In these animals about 180 grams of hemoglobin were removed in 1700 cc. of blood during 30 to 35 days before rapid regeneration ceased. This corresponds to the removal from their bodies of 0.57 gram of iron. If we grant a small intake of iron with the food and water during this period, there was present a definite depletion of the body iron reserve in the animals at the beginning of the experiments. In feeding 4,000 grams of beef liver the

amount of iron administered, according to the analysis of Forbes and Swift (7), would be 0.328 gram. The recovery of 50 grams of hemoglobin would remove 0.168 gram from the animal's body. If these values represent the average results, it seems impossible to recover the iron quantitatively when absolute iron starvation is present. The figures here quoted are conservative, and a proper conception of their significance is prerequisite to an appreciation of the conditions under which the experiments were carried out.

A sharp distinction must be drawn between cellular regeneration and hemoglobin formation in the bone marrow, and a knowledge of the number of reticulated red blood cells in the circulation is of fundamental importance in this respect. The reticulocyte percentages were surprisingly low, considering the large hemorrhages which were survived. This observation is susceptible of two interpretations: (1) either the response of the bone marrow was equal to the stress caused by the hemorrhages, or (2) the bone marrow was rendered relatively inactive by some such factor as faulty diet, or disease in the animal itself. It is obvious that the latter could not have been present, because after the preliminary bleedings the number of red blood cells in the circulation quickly returned to about the normal level, regardless of the dietary ingredients, and when iron was abundantly provided hemoglobin regeneration was not interrupted. It is evident that any definite stress placed upon the mechanism of healthy bone marrow to provide red blood cells would have been shown by a more pronounced increase in reticulocytes in the peripheral blood. For this reason, it must be assumed that the power of regenerating hemoglobin was alone being tested, and not the mechanism of cell production in the bone marrow.

A recalculation of the amount of hemoglobin regeneration in the experiments of Whipple and Robschey-Robbins has been made on the basis of grams of hemoglobin regenerated per day per kilogram of animal. The figures are taken from the experiments in which cooked beef liver and Bland's pills (2) (8) were used. In table 5 these recalculated figures are set down, together with the percentage of hemoglobin in the animals at the beginning, and at the completion of each experiment. It will be seen that in several of these experiments where the effect of liver feeding was sought, the animals lost

more than 25 per cent in the hemoglobin level during the progress of the experiment

For illustration, referring to table 5, dog 19-104, in the first experiment 0.360 gram of hemoglobin was regenerated daily per kilogram of dog, but the animal lost 38 per cent in its hemoglobin level during the four weeks period. In another experiment on the same animal, the regeneration rate, as calculated from the records, is 0.142 gram, the loss in hemoglobin being 16 per cent. In the five experiments in table 5, in which Bland's pills were administered during one-half

TABLE 5
Analysis of the results of Whipple and Robschert-Robbins

Dog number	Days	Added to diet	Average weight of dog	Total grams hemo globin re generated	Grams hemo globin re generated per day per kilo gram of animal	Hemoglobin level		
						Begin ning of experi ment	End of experi ment	Differ ence
			kgm			per cent	per cent	per cent
19-104	28	Liver	10.5	108.1	0.360	86	48	-38
19-104	28	Liver	11.0	43.7	0.142	52	36	-16
21-64	28	Liver	14.4	73.9	0.207	80	55	-25
16-160	28	Liver	10.8	36.4	0.120	57	48	-9
20-104	28	Liver	9.6	56.3	0.209	58	45	-13
20-104	28	Liver	8.7	98.8	0.396	74	47	-27
20-71	28	Liver	16.0	64.1	0.144	48	50	+2
20-104	28	Bland's pills	8.5	45.3	0.190	44	76	+32
20-71	28	Bland's pills	11.7	35.6	0.108	53	43	-10
21-64	28	Bland's pills	14.5	61.9	0.152	80	44	-36
24-3	28	Bland's pills	12.1	35.2	0.105	51	44	-7
24-2	28	Bland's pills	12.3	41.4	0.120	44	46	+2

the experimental period, only three of the experiments are susceptible of interpretation, for the reasons given above. The results of the experiments in which the hemoglobin level remained at about a constant (table 5) are quite comparable with those recorded here, and no fundamental disagreement in conclusions need be drawn.

It must be evident then from the results of both sets of experiments that the feeding of liver had no demonstrable effect in the regeneration of hemoglobin in anemia of long duration in healthy animals, when there was an adequate intake of iron.

The conclusions of Whipple, Robschert-Robbins, and Hooper (1),

regarding the effect of liver feeding proved successful fortunately, when applied to patients with pernicious anemia (9) The theoretical reason for this application is not clear, since the two conditions under which liver feeding must exert its action are totally different The predominate cell of the bone marrow in hemorrhage is quite different from the predominate cell of pernicious anemia in relapse The conditions imposed by these experiments upon the red blood cell production were at no time severe, and there was no evidence of delay in the development of red blood cells by the bone marrow, such as occurs in pernicious anemia In these experiments, even under relative iron depletion the number of red blood cells tends gradually to approach normal (See protocol, dog 3) Thus, we have no experimental or theoretical evidence that the administration of relatively enormous amounts of liver to the dogs could have a favorable effect upon red blood cell production

This paper has to do chiefly with hemoglobin regeneration, and further experiments are now in progress upon the phase of red blood cell regeneration

I am greatly obligated to Dr Sarah Long for her assistance in staining blood smears and making reticulocyte counts

CONCLUSIONS

1 In the presence of an adequate diet, hemoglobin regeneration in the long continued experimental anemia of healthy adult dogs is limited by the availability of iron

2 In this form of anemia the administration of liver has no specific action upon the regeneration of hemoglobin and acts entirely through its iron content

3 Liver feeding caused no demonstrable increase in red blood cell production, such as occurs in pernicious anemia

4 The therapeutic value of iron salts in the treatment of anemia resulting from hemorrhage is sustained

5 A sharp distinction must be drawn between hemoglobin formation and cellular regeneration of the blood elements in this type of anemia

6 Hemoglobin formation is depressed by relative iron starvation in long continued experimental anemia induced by hemorrhage, red blood cell production is somewhat less modified

PROTOCOLS

Date	Weight	Hema- tocrit	Red cell counts	Hemo- globin level	Amount bled	Reticu- loeytes	Oxygen capacity	Hemo- globin	Experimental diet
Dog No 70									
1927	kgm	per cent	millions	per cent	cc	per cent	voltimes per cent	grams	
March 21	14 6			130	275	1 2		50	
March 23				111	260		20 5	40	
March 25				88 7	230		16 4	28	
March 28		20	4 496	65	200	3 2	12 1	18	
April 1		16	4 104	39	20	7 2	7 1	1 0	Yeast—nucleic acid— FeCO_3 —0 6 gram
April 6		23	4 592	60	30	7 2	11 5	2 6	
April 8		27	6 544	64	65	7 0	11 9	5 7	Yeast—nucleic acid— FeCO_3 —0 6 gram
April 11	13 5	23	6 192	60	165	12 1	11 5	13 4	Yeast—nucleic acid— FeCO_3 —0 6 gram
April 12									Yeast—nucleic acid— FeCO_3 —0 6 gram
April 15		29	6 304	62 7	180	13 2	11 6	8 1	Diet—ferrie citrate
April 18		28	5 240	60	160	8 2	13 2		Diet—ferrie citrate
April 20			5 808	59	150	7 8	11 0	12 8	Diet—ferrie citrate
April 25			5 776	52	155	5 4	9 6	11 2	Diet—ferrie citrate
May 2		20	6 928	55 7	40		10 3	3 0	Diet—ferrie citrate
May 6	14 3	23	7 808	68 5	130		12 6	12 0	Diet—ferrie citrate
May 11		30	7 408	70	220	5 6		21 0	Diet—ferrie citrate
May 16	14 3	30	7 360	50	180	6 5	9 3	12 4	Diet—ferrie citrate
May 20				62	160	6 2		13 0	Diet—ferrie citrate
May 27			6 986	65	200	5 6		18 0	Diet—ferrie citrate
June 1	14 5		7 840	60	30	5 1	11 1	2 5	Diet only
June 6		24	5 450	52	200		9 6	14 3	Diet only

Dog No 8									
June 8	13 8	26	6 904	47	30		8 7	2 0	Liver—400 grams
June 13			6 368	50 3	200		9 3	13 8	Liver—400 grams
June 20		26		49	215		9 1	15 4	Diet only
June 26			5 948	46 5	200		8 6	12 8	Diet only
July 4			5 216	45	100		8 3	6 2	Diet only
Dog No 8									
March 30	12 3	34		113 6	275		21	43	Diet only
April 4			5 776	82	225		15 3	25 6	Diet only
April 8		27		75	200	7 4		20 7	Diet only
April 11	12 8		4 840	55	200	5 0	14	15 2	Diet only
April 15		27	5 392	75 7	30	3 8		2 6	Diet only
April 18	13 6		4 816	76	130	6 6		13 6	Diet only
April 25			5 840	78	200	2 2		21 5	Diet only
April 27			5 632	66	155	3 8		14 0	Diet only
April 29			4 928	66	150	6 3		14 0	Diet only
May 2			4 256	53 5	110		9 9	7 4	Diet only
May 4	13 2	24	4 240	55 2	30	6 0	10 2		Ferric citrate—0 8 gram
May 9			5 336	54	100	4 0	10 0	7 4	Ferric citrate—0 8 gram
May 13			7 072	61			11 3	12 8	Ferric citrate—0 8 gram
May 17	13 6	26	6 032	60	200	5 6	11 0	16 4	Ferric citrate—0 8 gram
May 20				52	160			11 5	Ferric citrate—0 8 gram
May 24		27	6 720	61	100		11 3	8 5	Ferric citrate—0 8 gram
May 27			6 996	62	200	4 5		17 0	Ferric citrate—0 8 gram
June 1	13 6		6 864	55	30	4 2	10 1	2 2	Ferric citrate—0 8 gram
June 3				53	130		9 6	9 3	Ferric citrate—0 8 gram
June 8	13 6	28	6 816	54	115		10 0	8 5	Ferric citrate—0 8 gram
June 10				57	30		10 5	2 0	Ferric citrate—0 8 gram
June 20				51 4	100		9 5	7 0	Ferric citrate—0 8 gram
June 26			7 168	63 3	150		11 7	13 0	Ferric citrate—0 8 gram
July 4				62 5	215		11 5	18 0	Ferric citrate—0 8 gram
July 11			7 808	63 2	40		11 7	3 0	Ferric citrate—0 8 gram

PROTOCOLS—Continued

Date	Weight	Hema- tocrit	Red cell counts	Hemo- globin level	Amount bled	Reticu- lyocytes	Oxygen capacity	Hemo- globin	Experimental diet
Dog No 69									
1927	kgm	percent	millions	percent	cc	percent	volumes percent	grams	
March 21	12 7			122	250	0 5		42	Diet only
March 23				92 8	240		17 2	30	Diet only
March 25				71	250		13 2	24 5	Diet only
March 28		20	4 992	59 5	180	7 0	10 9	14 8	Diet only
April 1		21	5 136	59 5	20		11 0		Liver 400 grams
April 6		24	5 616	72	140	7 7	13 3	13 9	Liver 400 grams
April 8		26		75	200			20 7	Liver 400 grams
April 11									Diet only
April 13	12 8	28	7 216	84	105	5 3	15 6	12 0	Diet only
April 16		28		73	130	3 8	13 5	13 0	Diet only
April 20				61	100			8 4	Diet only
April 25			6 192	68	85	3 2	8 0		Diet only
May 2		23	6 768	60	85	4 7	11 0	7 0	Diet only
May 6		21	6 816	68 5	130		12 6	12 0	Diet only
May 11	13 6		7 248	60	180	6 2			
May 13		23	5 680	45 7	80	7 4	8 45	5 0	Diet—nucleic acid—15 grams
May 16	14 8	25	6 320	47	200	18 7	8 7	13	Diet—nucleic acid—15 grams
May 20				50	200	12 1		15 8	Diet—nucleic acid—15 grams
May 25		25	5 360	43	170	14 2	8 0	10 2	Diet only
May 30		24	6 006	39	120	11 9	7 2	6 4	Diet only
June 6		23	5 460	41 7	30	5 5	7 7	2 0	Diet only
June 10				39 3	120		7 3	6 6	Diet only
June 20			7 888	45 4	120		8 4	7 5	Diet only

	Dog No 9					
June 26						Ferric citrate
July 4						Ferric citrate
July 11						Ferric citrate
July 20						Ferric citrate
July 25						Ferric citrate
April 22	12 0	8 000	116	200	1 8	Diet only
April 25			86	225	2 0	Diet only
April 27		6 160	94	50		Diet only
April 29			82	170	6 7	Diet only
May 1			78	75		Diet only
May 4				225		Diet only
May 9		4 344	52 4	150	9 3	Diet only
May 13	12 7				9 7	Diet only
May 18	22	4 448	53 5	40	9 5	Diet only
May 23	24	4 800	52 4	140	6 4	Diet only
May 30	25	6 112	48	30	5 3	Diet only
June 3	23	4 180	50 3	30		Diet only
June 9			53	110	9 3	Diet—ferric citrate—0 8 gram
June 13	11 8	5 520	54 1		9 6	Diet—ferric citrate—0 8 gram
June 20	26	6 432	66 5	150	10 0	Diet—ferric citrate—0 8 gram
	28		61 6	200	12 3	Diet—ferric citrate—0 8 gram
June 26		6 864	67 1	20	11 4	Diet—ferric citrate—0 8 gram
July 2			63 3	215	12 4	Liver 300 grams
July 8			62 2	200	11 7	Liver 300 grams
July 14			60	20	11 5	Liver 300 grams
July 20			65	100	11 1	Diet only
July 25		48	30		12 1	Diet only
					8 8	Diet only
					2 0	Diet only

PROTOCOLS—Continued

Date	Weight	Hema- tocrit	Red cell counts	Hemo- globin level	Amount bled	Relicu- loctes	Oxygen capacity	Hemo- globin	Experimental diet
Dog No 72									
	gms	per cent	millions	per cent	cc	per cent	volumes per cent	grams	
1927									
March 21	15.5			120	300	1.0	22.3	50	Diet only
March 23				98.5	190		18.2	27	Diet only
March 25				81.1	170		15	19	Diet only
March 28		23	4 064	73	150	4.3	13.5	15	Diet only
April 1		21	5 760	72	100			11	Diet only
April 6		23		76	150			16.5	Diet only
April 8		23	6 922	71	100	3.0	13.2	9.8	Diet only
April 13		24	5 992	74	200	4.2		21.8	Diet only
April 16		26		65	180	4.0	12.0	16.1	Diet only
April 18	14.8		5 720	50	40	4.9		2.6	Diet only
April 22	14.2		5 936	62	60	5.1	11.5	5.2	Diet only
April 25			5 584	56	150	1.0		11.6	Diet only
April 27			5 048	53	30	4.8		2.1	Diet only
April 29			4 768	58.1	20	6.7	10.7	1	Diet
May 4			5 696	50.1	100	4.7	10.0	7.5	Diet
May 10			6 184	51.3	115	5.9	9.5	7.1	Diet only
May 13		21	5 312	45.7	200	7.4	8.45	12.4	Diet only
May 11		19	4 976	39.1	200	6.7	7.24	10.8	Diet only
May 27	14.8		5 392	36	210	6.3		10	Diet only
May 30		22	5 300	34	30	5.9	6.35	1	Blaud's pills—10 per day
June 6			5 010	46	125	3.3	8.5	8	Blaud's pills—10 per day

June 10	15 0		61	160	11 4	13 6	Diet only
June 13		7 184	59	150	10 9	12 2	Diet only
June 20		6 144	42	210	8 3	13 2	Diet only
June 22		6 432	46	30	8 5		Ferrie citrate—nucleic acid—20 grams
June 29			57 4	240	9 5	17 0	Ferrie citrate—nucleic acid—20 grams
July 8			44 7	100	8 2	6 2	Ferrie citrate—nucleic acid—20 grams
July 14		5 688	38	160	7 1	8 5	Ferrie citrate—nucleic acid—20 grams

Dog No 2

December 28	11 6	40	102	225		31	Bread and milk
December 30		32	72	240		24 8	Bread and milk
January 4		24	70	200		19 3	Bread and milk
January 6			50	20			Thymus—400 grams
January 8		23	3 744	53			Thymus—400 grams
January 11		24 5	3 184	47		14 2	Thymus—400 grams
January 13		20	3 520	57			Thymus—400 grams
January 15		22	3 568	62		17 1	Thymus—400 grams
January 18	11 0	21 5	3 056	54			Bread and milk
January 22		20 5	4 200	56		11 6	Bread and milk
January 25		18 5	4 344	56		11 2	Bread and milk

Dog No 3

January 20	11 0	38	108	225			Bread and milk
January 22		32	88	250			Bread and milk
January 25		30 4	75	240			Bread and milk
January 27			5 000	30			Liver—400 grams
January 29		26 4	5 400	60			Liver—400 grams

PROTOCOLS—Continued

Date	Weight kgm	Hema- tocrit	Red cell counts	Hemo- globin level	Amount bled	Reticu- locytes	Oxygen capacity	Hemo- globin	Experimental diet
Dog No 3—Continued									
1927					cc	percent	cc/gram per cent	grams	
February 1		23 0	5 184	62	160			13 7	Liver—400 grams
February 5			5 056	56	140			10 8	Liver—400 grams
February 6									Bread and milk
February 10	11 8	20	5 312	50	30				Bread and milk
February 14		24	4 176	60	20				FeCO ₃ —0 6 gram
February 18		25 4	6 248	65	325			29 1	Thymus—400 grams
February 23				58	30			2 4	Thymus—400 grams
February 25									Diet only
February 28		27 5		70	75			7 2	FeCO ₃ —0 6 gram
March 2		26 8		67	240			22 9	FeCO ₃ —0 6 gram
March 4		19	5 272	48	30				FeCO ₃ —0 6 gram
March 9	13 2	23 3	6 744	67	40				FeCO ₃ —0 6 gram
March 14		25 4	6 992	66	220		12 2	20	Diet only
March 16			5 357	50	15	0 7			Diet only
March 21		22	5 960	54	40	2 7		3 0	Diet only
March 35		21	5 944	55 7	75	2 3	10 3	5 8	Diet only
March 30			7 224	62 3	30	3 5	11 5	2 6	Diet only
April 4		24	7 024	52	30	2 3	9 6	2 2	Diet only
April 8		23	7 624	57	100	2 8	10 7	8 0	Diet only
April 11	13 0		5 928	50	15	1 4			Yeast—nucleic acid—15 grams
April 15		23	6 528	51 4	140	4 0	9 5	9 8	Ferric citrate—0 8 gram

April 18	13 4	26	7 008	66	115	3 9	10 5	Ferric citrate—0 8 gram
April 20			6 908	58	90	5 0	10 7	Diet—ferric citrate
April 25			6 568	63 4	165	4 0	11 7	Diet—ferric citrate
April 27			7 530	62	100	4 7	8 6	Diet—ferric citrate
April 29			5 072	55	165	6 3	12 6	Diet—ferric citrate
May 4	13 4		6 640	55	30	6 6	10 2	Diet—ferric citrate
May 8			7 856	68 7	125	3 4	12 8	Diet—ferric citrate
May 11		33	8 176	64	180	4 9	16	Diet—ferric citrate
May 13	12 7	26	7 120	54	40	5 3	10 0	Diet—ferric citrate
May 18			7 200	54 6	200	4 3	15 0	Diet—ferric citrate
May 23		27	6 656	54 6	100	2 9	10 1	Diet—ferric citrate
May 30			4 650	52 6	150	2 8	9 7	Diet—ferric citrate
June 6			8 660	66	125	4 0	12 4	Diet—ferric citrate
June 10				70	30		13 0	Diet—ferric citrate
June 17			8 568	72	210		21 0	Diet—ferric citrate
June 24				60 6			11 2	Diet—ferric citrate

Dog No. 4

February 1	11 1	36	8 290	100	200			Diet—FeCO ₃ —0 6 gram
February 3			5 750	75	115			Diet—FeCO ₃ —0 6 gram
February 5				68	160			Diet—FeCO ₃ —0 6 gram
February 8		18 4	3 750	52	135			Diet—FeCO ₃ —0 6 gram
February 10		20 0	3 960	50	30		2 0	Nucleic acid—15 grams
February 14		23 0	4 512	64	60		4 3	Nucleic acid—15 grams
February 16				65	75		6 7	Nucleic acid—15 grams
February 18		27 7	5 056	63	190		16 6	Nucleic acid—15 grams
February 21				56	30		5 0	Diet only
February 25	11 8	26 6	5 532	68	90		8 4	FeCO ₃ —0 6 gram

PROTOCOLS—Continued

Date	Weight	Hema- tocrit	Red cell counts	Hemo- globin level	Amount bled	Reticu- locytes	Oxygen capacity	Hemo- globin	Experimental diet
Dog No 4—continued									
1927	kgm	percent	millions	percent	cc	percent	volumes percent	grams	
February 28		24 0		65	100			9 6	FeCO ₃ —0 6 gram
March 2		23 7		61	300			25 2	FeCO ₃ —0 6 gram
March 4		19 7	4 568	52	40				FeCO ₃ —0 6 gram
March 7			4 936	53	35	7 6	7 8	2 6	FeCO ₃ —0 6 gram
March 11	12 2	20 0	4 256	62	170	2 5		14 5	FeCO ₃ —0 6 gram
March 14									Diet only
March 16			4 912	53	40	3 2			Diet only
March 25		20	5 232	47	100	2 7		6 6	Diet only
March 30			4 928	43	40	4 4			Diet only
April 4		21	4 720	38 5	30	1 0			Diet only
April 8		18	5 176	38	25	4 7		1 0	Diet only
April 10	12 2								Diet—ferroc citrate
April 13		22	5 360	52 1	30	5 2	8 74	2 0	Diet—ferroc citrate
April 18	12 7	27	6 632	64	75	4 8		4 2	Diet—ferroc citrate
April 20			6 652	62	150	6 7		12 8	Diet—ferroc citrate
April 25			6 992	66 5	150	3 8		13 8	Diet—ferroc citrate
April 27			6 182	65	160	3 4		14 0	Diet—ferroc citrate
April 29			6 508	56	160	6 7		12 0	Diet—ferroc citrate
May 4	12 2	30	5 312	57	30	7 0	10 4		Diet—ferroc citrate
May 9			7 184	61 6	100	4 2	11 4	8 5	Diet—ferroc citrate
May 11		32	7 584	67	220	4 1		20 0	Diet—ferroc citrate

May 18	12 0	29	6 896	57	200	3 8	10 5	15 7	Diet—ferric citrate
May 23			7 152	61	200	5 8	11 3	16 8	Diet—ferrie citrate
May 25			6 400	54	30	10 1	10 0	2 0	400 grams liver—ferric citrate
May 30		27	5 280	49 2	150	7 8	9 1	10 2	400 grams liver—ferrie citrate
June 3				56 2	125	6 9	10 4	9 7	400 grams liver—ferrie citrate
June 5									Diet—ferrie citrate
June 8	13 0	32	6 890	60 8	125		11 2	10 5	Diet—ferrie citrate
June 13			6 580	64	180		11 8	15 8	Diet—ferrie citrate
June 20		30		63 6	210		11 7	18 2	Diet—ferrie citrate
June 22			6 128	65	30		12 1		Diet—ferrie citrate
July 2				63 8	30		11 8		Diet—ferrie citrate

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CIRCULATORY ADJUSTMENT IN ANEMIA

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Previous studies of the circulation rate in man in various types and degrees of anemia (1, 2, 3) have concerned themselves chiefly with comparisons of circulation rates of groups of anemic individuals with the rates of normal individuals.

Inasmuch as the normal rate varies greatly from one individual to another, it occurred to us that it might be of interest to study the cardiac output as well as other functions of the circulation of a given subject while in the anemic state and also at intervals during his recovery. It would thus be possible to show in that individual the adjustment to the condition of anemia, and a group of such studies might give a clearer picture of the adaptive process than could be obtained from purely statistical data on circulation rates and related functions.

The present investigation is a study of the cardiac output in eight anemic subjects both during the stage of anemia and at intervals in the period of recovery. The initial oxygen capacities of the blood varied from 5.4 to 14.4 volumes per cent. Two were suffering from primary anemia, four from secondary anemia following hemorrhage from gastric or duodenal ulcer, one from secondary anemia with carcinoma of the stomach, and one had a secondary anemia associated with purpuric manifestations. When the experiments were made, the subjects were in all instances apparently well compensated to their anemia, while at rest in bed, temperature, respiratory rate and pulse rate were within normal limits except that on two occasions the pulse was as high as 90. All experiments were done in the morning, under basal conditions—that is, after at least 12 hours without food, and half an hour of complete rest in bed.

The data which were measured in each experiment were (1) alveolar and oxygenated "mixed venous"¹ CO₂ tensions, (2) minute volume, and O₂ and CO₂ percentages, of expired air, (3) CO₂ dissociation curve of venous blood, (4) oxygen capacity of venous blood

From these data were calculated (5) cardiac output per minute (Field-Bock method), (6) arterial and venous serum pH, (7) oxygen consumed per 100 cc of blood, (8) oxygen consumed per cent of capacity, (9) basal metabolic rate and, (10) respiratory quotient

METHODS

For the measurement of cardiac output per minute, our method was essentially that of Field, Bock, Gildea and Lathrop (5), with a few modifications in apparatus

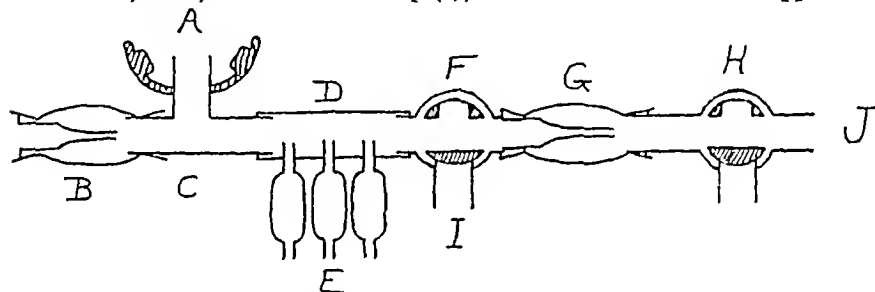


FIG 1 DIAGRAM OF MODIFIED FIELD-BOCK APPARATUS FOR MEASURING CARDIAC OUTPUT, FOR PORTABLE USE

A, mouthpiece, B, intake flutter valve, C, brass "T" tube, D, rubber tubing, E, gas sampler vessels, F and H, 3-way valves, G, flutter valve, I, opening for attachment of rebreathing bag, J, opening for attachment of Douglas bag

which we made chiefly for purposes of compactness, in order that the apparatus might be easily portable on the wards

The apparatus is illustrated diagrammatically in figure 1 To the base of a small "T" tube of $\frac{3}{8}$ -inch brass tubing is fitted the rubber mouthpiece To one arm of the "T" tube is attached a flutter valve, the valve being brought as close as possible to the mouthpiece tube, in order to diminish the dead space To the opposite arm of the "T" tube is attached a piece of stiff rubber tubing, perforated by three small holes for the insertion of the ends of gas sampler vessels Beyond the rubber tubing are attached, successively, a three-way valve, a second flutter valve, and another three-way valve

¹ By this phrase is meant the CO₂ tension of mixed venous blood, estimated from modified alveolar air presumably in equilibrium with mixed venous blood in the pulmonary capillaries

The gas samplers were glass vessels of 25 to 30 cc. capacity, with a stopcock at each end. They were arranged in sets or batteries of three, each set fastened to a wooden back for support and attached by glass tubing and a length of about 75 cm of rubber pressure tubing to a single thistle tube of mercury. With this,

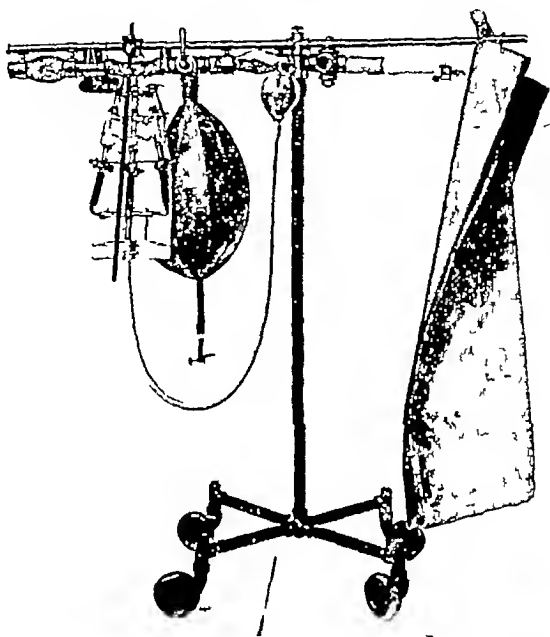


FIG 2 MODIFIED FIELD-BOCK APPARATUS FOR MEASURING CARDIAC OUTPUT, FOR PORTABLE USE

In actual use, the gas samplers are tipped up horizontally, to lift them above the bed or subject's body

all three samplers could be evacuated by a single lowering of the mercury. As far as ease and rapidity of collection of samples are concerned, the advantage of having a Torricellian vacuum in the sampling tubes is obvious.

To the side opening of the first three way valve, the re-breathing bag containing

the $\text{CO}_2\text{-O}_2$ mixture was attached, and to one opening of the three-way valve at the end, a Douglas bag of 100 liters capacity

The whole apparatus was suspended on a small stand provided with rollers (fig 2)

The technique which we used for estimating the cardiac output was as follows the rebreathing bag was first filled with a mixture of CO_2 and O_2 . Inasmuch as, during rebreathing, the CO_2 in the bag is considerably diluted by the residual air in the subject's lungs, we used an initial tension in the bag which when diluted with the residual air would bring the resultant mixture to about the tension of the oxygenated "mixed venous" blood, and thus prevent the necessity of the blood's either absorbing or giving up considerable amounts of CO_2 .

Since the oxygenated "mixed venous" tensions of CO_2 varied usually between 42 and 50 mm, the ideal initial tension for CO_2 in the rebreathing bag would be somewhere between 45 and 55 mm, we therefore used as the initial tension in the bag for our experiments approximately the mean of these tensions, that is to say, 48 to 50 mm or about 7 per cent CO_2 . From 2.5 to 4 liters of the $\text{CO}_2\text{-O}_2$ mixture were used in the rebreathing bag, depending on the patient's probable vital capacity. The subject, as stated, was under basal conditions, lying in bed, with head and body at an angle of 30 degrees or less from the horizontal. The apparatus having been adjusted to the patient and a few minutes having been allowed for him to become accustomed to it, expired air was then collected for six or seven minutes in the Douglas bag. The volume of air in the bag was immediately measured, and a sample taken for analysis. At the end of a normal expiration, a rubber cork was inserted into the end of intake valve B (fig 1), plugging it completely, and the subject told to make a complete expiration. Toward the end of this expiration, one of the evacuated sampler tubes was opened, and the alveolar sample sucked in. The cork was then removed from the flutter valve. After three minutes, the same procedure was repeated, except that immediately after the alveolar sample was obtained, the valve F was opened into the rebreathing bag, and the subject rebreathed the $\text{CO}_2\text{-O}_2$ mixture four times within 20 seconds. Toward the end of the fourth rebreathing the third evacuated tube was opened, and immediately thereafter the valve F turned again and the cork removed from the intake flutter valve. A sample of the contents of the rebreathing bag was then taken.

After a few minutes' rest, this entire procedure was repeated. Thus at the end of the experiment, there were obtained for analysis four alveolar air specimens, four "mixed venous" specimens, and two six- or seven-minute volumes of expired air.

This technique involving as it did several variations from that described by Field, Bock, Gildea and Lathrop, it was necessary to check our method in various ways. Air samples obtained by evacuated tubes and by ordinary sampling tubes were found to be the same. By the use of evacuated tubes, we investigated the effect of rebreathing from the $\text{CO}_2\text{-O}_2$ bag by taking samples after each rebreathing, and we found, as others have done, that the samples after the third and fourth

rebreathings were practically the same, and were the same as the contents of the bag after rebreathing. We next compared the alveolar airs obtained by our method with Haldane Priestley samples, in order to ascertain whether the air enclosed in the dead space in flutter valve B would be partly sucked into the sampling tube and dilute the sample. This was found to be the case, these alveolar airs being an average of 0.4 mm. lower in CO_2 tension than the Haldane-Priestley samples. By filling in as much of the dead space in flutter valve B as possible with plasticine clay, this discrepancy was reduced to an average of 0.25 mm.

In order to test the apparatus further, alveolar airs were compared directly with arterial blood. A series of alveolar air samples was taken, usually five, using the apparatus as described above, and during this procedure arterial blood drawn. To avoid as far as possible changes in pulse rate and respiration during the drawing of blood, the method of Goldschmidt and Light (6) was used, one hand being immersed in hot water for 10 minutes, and blood then taken from a hand vein into a vessel containing oil and enough dried neutralized potassium oxalate to make a final concentration of about 0.2 per cent. Blood so obtained was in every case between 94.5 and 96 per cent saturated with oxygen and so presumably practically identical with arterial blood, as Goldschmidt and Light also found. The arterial CO_2 content was measured, a CO_2 dissociation curve constructed with oxygenated blood, and the average alveolar air tension compared with the tension on the 95 per cent oxygenated CO_2 curve, at the point determined by the arterial CO_2 content. In a series of six such measurements, the alveolar air CO_2 tensions varied from the arterial as follows: -1.4 mm., +0.3 mm., -2.2 mm., -0.3 mm., -1.5 mm., and 0 mm., an average of -0.85 mm. In a similar series of 15 measurements by Field, Bock, Gildea and Lathrop, an average of -0.48 mm. was obtained. It is thus likely that the apparatus which we used gave alveolar air specimens that were about 0.3 mm. lower than those obtained by the original Field Bock method.² We have, however, retained the 1.0 mm. correction factor used by these authors, for the reason that the discrepancy is small, and the further reason that the difference in level between the arterial and the completely oxygenated blood CO_2 curve, which accounted for 0.5 mm. of this correction factor, is probably less in anemic bloods, since 5 per cent unsaturation in anemic blood would cause less displacement of the CO_2 curve than 5 per cent unsaturation in normal blood.

We made several attempts to obtain arterial blood samples from the subjects during or just after the estimations of cardiac output but in most instances were unable to do this without definite changes in the subject's pulse rate and respiration. Two such attempts in which there was relatively little change in these factors (first experiments on J K. and on J H.) gave arterial blood tensions that were -2.8 mm. and +1.8 mm. respectively from the mean alveolar air tensions.

² A modification of the apparatus has been made wherein a small slide valve is inserted between flutter valve B and the mouthpiece thus enabling more exact Haldane-Priestley alveolar air samples to be taken.

Since the Field-Bock method gives arterial and venous CO_2 tensions, which have to be transferred into terms of CO_2 contents by the use of the slope of the CO_2 curve, it was necessary in these experiments to determine the CO_2 curve on each occasion, because the slope of the curve varies chiefly with the hemoglobin content of the blood. In all our later experiments, the curve was constructed from 2 points, usually about 25 and 50 mm tensions, using logarithmic paper and Peters' straight line logarithmic relation. In some of the earlier experiments, three or more points were determined. In four instances, CO_2 curves were not constructed, and the slopes only estimated (table 1).

Gas analyses were made with the Haldane apparatus, the blood gas analyses by the Van Slyke-Neill apparatus. The technique of equilibrating and handling blood samples was that of Austin, Cullen, Hastings, McLean, Peters and Van Slyke (19) with a few slight modifications.

With the CO_2 curves which we were constructing, it soon became evident that the slope was in most cases nearly a direct function of hemoglobin concentration. This relationship was established by Peters, Bulger and Eisenman (7) a few years ago, in a large number of experiments. Using CO_2 contents at 30 and 60 mm. tensions, these authors found that the differences between the contents at these two tensions, for varying oxygen capacities, could be represented approximately by the formula

$$\Delta [\text{CO}_2]_{60/30} = 0.334 h + 6.3$$

where h = oxygen capacity in volumes per cent. This difference in CO_2 content at constant tension difference is a measure of the slope of the curve. If, therefore,

one uses this relation in the form of a ratio, $\frac{0.334 h + 6.3}{0.334 (20) + 6.3}$ and multiplies this

ratio by the standard slope values for normal blood (oxygen capacity of 20 volumes per cent) as given by Field, Bock, Gildea and Lathrop, the product will be a fairly close approximation to the actual slope of the CO_2 curve for blood of oxygen capacity h . We have calculated these values for each experiment (table 1). The agreement with the actual CO_2 curve slopes is good, the difference being less than 10 per cent in every case but one. Comparing our findings in this respect with the fifty-one experiments of Peters, Bulger and Eisenman, on which the formula is based, it was found that our results showed less marked deviations than did theirs. The scattering of the points in their experiments, however, as they themselves pointed out, occurred to a much greater degree with bloods of high oxygen capacity than with low. If the thirteen experiments which these authors made using bloods of less than 14 volumes per cent oxygen capacity are considered, it is found that all the points fall close to the line determined by their formula (the deviation being less than 10 per cent) except one. In future investigations of anemic bloods, the use of the adaption of this formula with the Field-Bock value for normal slope of the CO_2 curve, may be expected, therefore, to give results at least as accurate as would the use of these "normal" values for different bloods of normal or nearly normal oxygen capacities.

It has been recognized for some time that the accuracy of the gasometric method of calculating cardiac output depends on the accuracy of estimating its most variable element, namely, the alveolar air measurements. In studying untrained subjects, we have in this respect, encountered some difficulty at times. Frequently one, and occasionally more than one, of the four alveolar air measurements was quite far from the others, so for calculating both alveolar air and "mixed venous" tensions we adopted the method of the mean, discarding the highest and lowest figures and taking the average of the middle two. In order to give some idea of the error of the method we have in table 1 included both of the two mean alveolar air determinations of each experiment.

For a reason which will be discussed presently, it was of interest to us to calculate the pH of arterial and venous serum for each experiment. The arterial point was taken as the point on the oxygenated CO_2 curve determined by the level of the mean alveolar CO_2 tension, the pH being calculated by the Henderson Hasselbalch formula, using the method worked out by Peters, Bulger, and Eisenman (8). The actual arterial point is slightly above and to the right of the point from which our calculations have been made, but the difference in pH of the two points is negligible. The actual "mixed venous" point on the diagram of the CO_2 dissociation curve lies on the line of the content of oxygenated "mixed venous" CO_2 , but to the left of the oxygenated CO_2 curve. This distance is such that the point lies above that curve by an amount determined by the oxygen unsaturation of the venous blood. Since we have measured the utilization of O_2 per 100 cc. of blood,³ and since we know from the work of Bock, Field, and Adair (9) the number of volumes per cent CO_2 taken up in complete reduction of normal blood at constant CO_2 tension (about 6.2 volumes per cent) it is easy to calculate approximately the loss of CO_2 tension of the actual mixed venous blood due to oxygen unsaturation. This formula is

$$p(\text{CO}_2) = p(\text{CO}_2) - \left(\frac{\Delta\text{O}_2 \text{ cc.}}{20} \times 6.2 \right) \left(\frac{1}{s} \right) - 0.5$$

where $p(\text{CO}_2)_a$ = actual mixed venous CO_2 tension, $p(\text{CO}_2)$ = CO_2 tension of oxygenated mixed venous blood, s = slope of the CO_2 curve and ΔO_2 cc. = tissue utilization of oxygen per 100 cc. of blood. The figure 6.2 has been explained, and 20 is the total volumes per cent oxygen unsaturation of normal reduced blood. The last figure, 0.5, is the approximate difference in tension between completely oxygenated and arterial (95 per cent oxygenated) blood.

Metabolic rate calculations have been made using the DuBois height weight surface area relation, and the value of 4.8 calories per liter of O_2 per hour, irrespective of the respiratory quotient.

³ This is obtained from the difference in CO_2 content of arterial and venous blood by dividing by the respiratory quotient.

RESULTS

On the eight individual subjects, twenty-two observations in all were made (Table 1 and charts A to F of figure 3). The general results of the investigation are readily seen from these charts: (a) there is a definite though not entirely constant tendency for cardiac output to increase with decreasing hemoglobin concentration, (b) a practically constant increase of percentage utilization of oxygen by the tissues (ΔO_2 per cent) with increasing anemia, especially noticeable between 10 and 6 volumes per cent oxygen capacity, (c) a tendency to decrease of tissue utilization of oxygen per 100 cc of blood (ΔO_2 cc), with decreasing oxygen capacity, (d) a relative increase in metabolic rate when the anemia is pronounced, (e) a tendency toward lowered respiratory quotient, which frequently rises as the oxygen capacity increases, (f) increased ΔpH in severe anemia.

To summarize, as far as the data here presented are concerned, the general statement may be made that in the state of anemia, the burden, as it were, that is laid upon the rest of the circulatory apparatus as a result of diminished oxygen capacity, tends to be distributed, a part being taken by an increase in the cardiac output per minute and a part by increased percentage utilization of oxygen by the tissues. There are individual variations, the increased utilization at times taking almost all the burden. This appears particularly in the first experiments on F. L. and S. D. two primary anemias of long standing. Subject F. L. at this time was slightly edematous and subject S. D. markedly so, the latter's whole circulatory adjustment during her extreme anemia was in fact quite different from any of the others, and suggests beginning heart failure. The final experiment on this subject, however, shows an even more striking deviation from the rest of the group. There is reason to believe that in part at least this was due to faulty technique. The CO_2 - O_2 mixture in the bag before rebreathing, was lower in CO_2 tension than the subject's own oxygenated "mixed venous" tension. Evidence that equilibrium was not reached during rebreathing is given by the fact that the tensions of the samples taken at the end of the fourth rebreathing were 0.9 and 0.7 mm. higher than the samples taken from the bag afterward. If equilibrium was not reached the CO_2 tension difference between

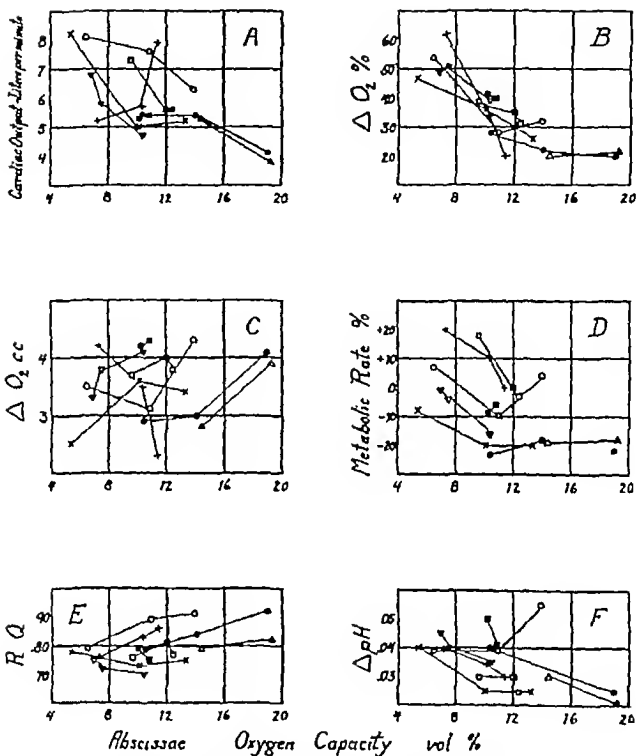


FIG 3 CHANGES IN CIRCULATORY FUNCTIONS IN ANEMIA

Abscissae in each chart represent oxygen capacities in volumes per cent ΔO_2 cc. = oxygen utilized by the tissues, in cubic centimeters per 100 cc. of blood ΔO_2 per cent = oxygen utilized by the tissues in per cent of capacity (coefficient of tissue utilization) ΔpH = difference between arterial and venous serum pH.

Symbols indicate individual subjects \bullet = F L \circ = J K. Δ = M H \square = J H. \blacksquare = W S ∇ = N B $+$ = S D \times = J J

TABLE 1

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Subject Sex Age	Date	O ₂ capac- ity	Pulse rate	Respi- ration	Venti- lation	CO ₂ ex- pired	O ₂ con- sumed	R:Q	Basal meta- bolic rate	Alveolar CO ₂	"Ve- nous" CO ₂	Ar- terial CO ₂ tent	Ar- terial pH	Ve- nous pH	CO ₂ curve slope Ob- served	CO ₂ curve slope Calcu- lated	ΔO ₂ cc*	ΔO ₂ per cent†	Car- diac out- put
		liters per cent	per minute	per minute	liters per minute	cc per minute	cc per minute		per cent	mm	mm	volumes per cent							liters per minute
F L	February 8	10 4	88	16	4 0	126	159	0 79	-23	39 4-39 4	48 7	55 1	7 41	7 37	0 28	0 32	2 9	28	5 4
F	February 26	14 0	70	14	5 4	137	164	0 84	-18	34 6-32 9	41 6	†			0 37	0 40	3 0	22	5 4
50	March 9	19 0	72	13	5 4	146	159	0 92	-22	38 6-38 8	47 9	43 6	7 345	7 32	0 43	0 43	4 1	20	4 1
J K.	February 16	6 5	90	18	8 2	220	280	0 79	+7	36 4-35 9	46 3	57 0	7 45	7 41	0 30	0 30	3 5	54	8 1
M	March 16	10 9	62	15	7 6	211	236	0 89	-10	39 1-38 7	48 0	54 4	7 41	7 37	0 34	0 34	3 1	28	7 6
46	April 19	13 9	68	17	9 7	251	275	0 91	+4	33 6-34 8	46 2	52 6	7 465	7 41	0 36	0 39	4 3	32	6 3
M H.	March 23	14 4	69	14	3 8	118	149	0 79	-19	40 6-40 8	48 1	50 4	7 37	7 34	0 35	0 38	2 8	20	5 3
F	May 20	19 2	68	13	4 1	124	151	0 82	-18	39 5-39 6	47 5	48 4	7 38	7 36	0 47	0 44	3 9	21	3 8
40																			
J H.	April 2	9 6	88	17	7 7	205	268	0 76	+19	36 0-36 3	44 7	48 8	7 39	7 36	0 37	0 34	3 7	39	7 3
M	April 26	12 4			6 6	166	216	0 77	-3	537 5-38 4	46 4	52 1	7 41	7 385	0 40	0 37	3 8	31	5 6
50	May 18	12 0	76	15	7 1	181	223	0 81	0	37 4-37 0	46 8	48 4	7 38	7 35	0 38	0 37	4 0	35	5 6
W S	April 14	10 2	84	18	6 4	176	223	0 79	-9	38 5-37 6	49 5	73 5	7 55	7 50	0 32	0 34	4 2	41	5 3
M	May 2	10 8	76	17	6 7	175	232	0 75	-6	34 8	44 8	46 7	7 39	7 35	0 36	0 35	4 3	40	5 4
49																			

N B	May 25	7 5	77	15	6 7	159	221	0 72	-4	37 7-36 2	46 9	53 27 41	7 37	§	0 31	3 8	51	5 8
M.	June 8	6 9	72	15	7 2	169	227	0 75	-1	33 5-32 3	41 7	51 87 445	7 40	§	0 32	3 3	49	6 8
50	June 20	10 4	56	14	5 5	135	193	0 70	-16	36 7-36 0	46 1	53 77 43	7 395	0 33	0 35	4 1	40	4 7
S. D	June 6	7 3	90	12	5 7	167	218	0 76	+20	34 9-34 2	46 0	50 77 40	7 36	0 31	0 31	4 2	62	5 2
F	June 24	10 3	68	9	5 0	165	200	0 83	+10	37 4-38 1	46 6	56 17 435	7 40	0 37	0 35	3 5	34	5 7
36	July 20	11 4	72	9	4 5	156	181	0 86	0	41 3-41 6	48 4	57 07 41	7 38	0 33	0 34	2 3	20	7 9
J J	June 16	5 4	68	13	5 7	160	207	0 78	-8	37 8-37 6	45 4	57 77 43	7 39	0 29	0 29	2 5	47	8 3
M.	July 6	10 1	55	12	4 9	130	178	0 73	-20	38 7-39 3	47 5	55 17 41	7 385	0 35	0 34	3 6	36	5 0
48	July 19	13 3	56	13	4 8	132	176	0 75	-20	38 3-38 4	46 0	53 57 42	7 395	0 38	0 39	3 4	26	5 2

* The data in column 18 = $\frac{\text{column 8}}{\text{column 20}}$

† The data in column 19 = $\frac{\text{column 18}}{\text{column 3}}$

‡ CO₂ curve not done, value of slope by interpolation.

§ Only 1 point on CO₂ curve determined slope by Peters formula

alveolar and "mixed venous" samples was too small and the cardiac output figure therefore too high. As there was no other evidence of error than this, however, the experiment was included with the others.

DISCUSSION

Of our general findings, (a), (b), (c) and (d) are entirely confirmatory of Liljestrand and Stenstrom's recent work on anemic subjects (3), using the Krogh-Lindhard nitrous oxide method, and are also consistent with Blalock and Harrison's (10) findings in dogs following repeated small hemorrhages.

Dautrebande (4) has recently reported a series of measurements of cardiac output, using Meakins and Davies' method, on a group of four subjects with anemia, at various stages of their disease. His findings were essentially these: at 20 per cent hemoglobin, two determinations, with cardiac outputs about 14 liters per minute, at 26 per cent hemoglobin one measurement, cardiac output 10.5 liters per minute, at 30 per cent hemoglobin, two measurements about 8 liters per minute, above 40 per cent hemoglobin, the cardiac outputs drop rapidly from 5 or 6 liters per minute to normal values, between 4 and 5 liters per minute. He followed one subject for several months, and found practically the same output on all occasions as long as the hemoglobin was above 50 per cent. Our data tend to show a continued fall in cardiac output with increasing oxygen capacity, they do not show, moreover, so sharp a rise in cardiac output between 40 and 25 per cent hemoglobin as do those of Dautrebande. Some of the discrepancy is probably due to the fact that the measurements made by Dautrebande were performed only 3 hours after the subjects' last meal, rather than under strictly basal conditions, and at these low levels of oxygen capacity a small increase in oxygen consumption would be expected to cause a considerable change in cardiac output.

Basal metabolic rates in anemia have been variously reported (DuBois 11), some investigators have found normal values, others an increase. Meyer and DuBois (12) in a very carefully conducted series of experiments on five cases of pernicious anemia, found the metabolic rate slightly raised in the mild cases, and distinctly raised in the severe cases. The only experiments which we have found in

the literature, in which individual subjects were studied during recovery from anemia, were those of Tompkins, Brittingham and Drinker (13), who found regularly a decrease in metabolic rate following transfusions

A lowered respiratory quotient has not, so far as we are aware, been noted by other investigators. The five cases reported by Meyer and DuBois had normal R Q s, except one, which was slightly low. Examination of the data in eighteen untreated cases of anemia as reported by Tompkins, Brittingham, and Drinker, however, shows that the respiratory quotients were all below 0.81, with an average of 0.75. Moreover, eight cases treated by transfusions, all showed a definite rise in respiratory quotient. These findings are in agreement

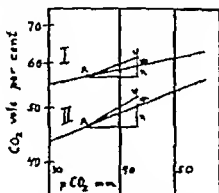


FIG. 4. CO_2 DISSOCIATION CURVES PLOTTED LOGARITHMICALLY

I, anemic curve (subject J. J.) *II*, normal curve (subject M. H. after recovery) *m*, increase of CO_2 content, oxygen unsaturation effect *n*, increase of CO_2 contents, buffer effect

with our data, it is perhaps of interest to note that all the cases in our series that showed significant rise in respiratory quotient during recovery were on a "liver diet."

In view of the general tendency mentioned above, to "distribute the load," it becomes of interest to inquire further, if possible, into the mechanism of the distribution. In this respect the change in shape of the CO_2 dissociation curve has certain consequences that may be pointed out. The flattening of the oxygenated and reduced curves, which occurs in anemic bloods, is presumably due to loss of cell proteins (chiefly hemoglobin), in their capacity as buffers. In the change from the arterial to the venous point, it can readily be seen from Figure 4 that if the CO_2 tension differences remain the same, and

ΔO_2 cc is the same for the two bloods, $\Delta[CO_2]$ will be considerably less in the anemic blood due to a decrease in the "cell-buffer" increment of n . In other words, the respiratory quotient will be diminished. To maintain a more nearly constant RQ , at least three adjustments are possible, (a) a decrease in ΔO_2 cc, (b) an increase in the arterio-venous CO_2 tension difference, or (c) displacement of both arterial and "mixed venous" CO_2 tension lines to the left, where the CO_2 curve is steeper. The decrease in ΔO_2 cc would, of course, involve an increased blood flow, supposing the oxygen consumption to remain unchanged.

There is a further consequence of the altered form of the CO_2 dissociation curve. Since the serum pH values on the dissociation curve diagram may be represented (following Y. Henderson) by straight lines radiating from the point of origin, it is obvious that a flattening of the CO_2 curve will involve increase in the pH difference between arterial and venous blood (increased ΔpH). This increase will tend to be accentuated if the arterio-venous CO_2 tension difference is increased, but diminished in proportion to the height of the curve above the base line. These considerations were pointed out several years ago by Barr and Peters (14). The net result is a distinct increase in the ΔpH in anemia. This was noted in Barr and Peters' work, and appears in our data. Increased ΔpH will, furthermore, increase the oxygen that can be taken up by the tissues at a given oxygen tension difference between arterial and venous blood, due to the lowering of the oxygen dissociation curves with increasing acidity. It is doubtful, however, if this effect on the percentage utilization of oxygen by the tissues will be a significant one, for two reasons, (1) reference to oxygen dissociation curves will show that such changes in ΔpH as occur in anemia (table 1) are sufficient to increase the utilization at given O_2 tension differences by only 3 or 4 per cent of the oxygen capacity at the most, (2) the actual effect is probably even less than this, since, according to the work of Barr and Peters, and others, the change in pH in anemia is usually due to a more alkaline arterial pH rather than a more acid venous pH. As the O_2 dissociation curves for different pH values are quite close to one another in the region of arterial saturations, small changes in acidity would

produce correspondingly small changes in oxygen saturation, at constant oxygen tension

When the percentage tissue utilization of oxygen is appreciably increased, therefore, there will be associated a diminished mean capillary oxygen tension, and presumably a diminished tissue oxygen tension. Decreased oxygen tension, as Krogh (15) has shown, produces both capillary and arterial dilatation. Liljestrand and Stenström (3) have called attention to the fact that increased percentage tissue utilization is consistent with increased capillary surface. Total cardiac output on the other hand, would be expected to increase, since this is the first effect of vasomotor (especially arterial) dilatation (Tigerstedt (16)). There is thus the possibility of a balanced relationship between cardiac output on the one hand, and mean capillary or tissue oxygen tension, or, what in this case amounts to the same thing, percentage tissue utilization, on the other. This proposition was suggested in part by Blalock and Harrison (10).

Blood pressure measurements unfortunately were not made in our series. Liljestrand and Stenström (3) found the mean arterial blood pressures to average 4 to 11 mm less in anemic subjects than in normal subjects. This is a small difference but is consistent with increased cardiac output and arterial dilatation, since according to Poiseuille's law an inverse relation between pressure and flow may exist providing there is simultaneously a small change in diameter of the channels of flow.

Between rates of 60 and 90, increased pulse rate would be expected to produce increased cardiac output (17), other things being the same, and venous inflow to the heart being adequate. But if increased pulse rate were the dominant factor here—the peripheral blood vessels remaining unchanged—, one would expect an increased mean blood pressure.

Other factors concerned in estimating the magnitude of cardiac output in anemia are viscosity, and total blood volume. Viscosity is, of course, decreased, tending to increase cardiac output and decrease blood pressure, total blood volume is usually diminished (18) which will tend to decrease cardiac output.

It is clear from the data which we have charted, that the circulatory adjustments which actually take place in anemia are those which

have suggested themselves in the preceding discussion, (1) lowered respiratory quotient, either absolute, or relative to subsequent values, (2) increased ΔpH , tending to diminish as the oxygen capacity increases, (3) decreased ΔO_2 cc and increased ΔO_2 per cent, and (4) increased cardiac output. In this series, there was no consistent change in the arterio-venous CO_2 tension difference in anemic as compared with normal blood.

That the above changes may be influenced by numerous factors other than those we have discussed, is obvious. One would not expect, for example, that so complex a function as the respiratory quotient would be largely determined by the form of the CO_2 dissociation curve.

In extreme anemia, ΔO_2 per cent apparently approaches an upper limit. With this function no longer increasing, any further fall in oxygen capacity must result in a sharp decrease in ΔO_2 cc, and a corresponding rise in blood flow. These changes begin to be apparent in the first experiment on J. J. They are brought out still more clearly by Dautrebande's measurements (4), already referred to in subjects with only 20 per cent hemoglobin.

Our data, so far as we can see, do not throw any light on the fact of increased metabolic rate in severe anemia. Other investigators have ascribed this increase either to increased cardiac work attendant on increased output, or else to increased bone marrow activity. Tompkins, Brittingham, and Drinker (13) were inclined to the latter explanation since in their studies, the rate diminished following transfusions. Of the five cases in our series in which the metabolic rate decreased with improvement of anemia, four received transfusions during the interval, while in one case (S. D.) the rate dropped on "liver diet" alone.

SUMMARY

1. Studies of cardiac output and certain other functions of the circulation, have been conducted on eight subjects suffering from various types and degrees of anemia, the observations on each individual having been made both during the anemic state and after partial or complete recovery.

2 In this series, there was a tendency for the following changes to occur during the anemic state

- a Increased cardiac output.
- b Increased percentage utilization of oxygen by the tissues
- c Decreased utilization of oxygen by the tissues in cubic centimeters per 100 cc. of blood
- d In five instances, a relative increase in metabolic rate during severe anemia
- e Low respiratory quotient, frequently this increased during recovery from anemia
- f Increased ΔpH (difference between arterial and venous serum pH)

3 Of these changes, (c), (e) and (f) are shown to be consistent with the change in form of the CO_2 dissociation curve in anemia. A balanced relationship between cardiac output (a) and the percentage tissue utilization of oxygen (b) is possible, on the basis of vasomotor dilatation and lowered blood pressure in the anemic state. Blood pressure has been reported as lowered in anemia, vasomotor dilatation is to be expected when, as here, mean capillary or tissue oxygen tension is decreased.

4 A slightly modified Field-Bock method for measuring cardiac output, with portable apparatus, is described.

PROTOCOLS

F L Female, age 50 Diagnosis Pernicious anemia.

History Numbness and tingling of hands and feet for 18 months, weakness, dyspnea on exertion and edema of ankles for one year

Physical examination Pallor, deep reflexes hyperactive, legs spastic, slight edema of feet

February 4 Red blood cells 1,400,000, hemoglobin 36 per cent

February 22 Red blood cells 3,200,000, hemoglobin 68 per cent.

March 9 Red blood cells 4,300,000, hemoglobin 62 per cent (?)

Course Striking improvement on liver diet.

J K Male, age 46 Diagnosis Secondary anemia, purpura.

History Dyspnea and weakness for one year, dizzy spells for one month

Physical examination Pallor, hemorrhagic areas on legs, eye ground hemorrhages

February 13 Red blood cells 1,400,000, hemoglobin 29 per cent.

February 18 Transfusion 800 cc

March 8 Red blood cells 2,400,000, hemoglobin 45 per cent

April 18 Red blood cells 2,800,000, hemoglobin 57 per cent

Course Gradual improvement with one transfusion and liver diet

M H Female, age 40 Diagnosis Ulcer of stomach, secondary anemia

History Sleepiness for two months, fever, nausea and vomiting for four weeks, fainted ten days before

Physical examination Pallor, stool guaiac + + + + X-ray penetrating ulcer of lesser curvature of stomach

March 23 Red blood cells 3,000,000, hemoglobin 59 per cent

March 29 Transfusion 500 cc

May 16 Transfusion 400 cc

May 19 Red blood cells 4,900,000, hemoglobin 86 per cent

Course Gradual improvement and disappearance of symptoms with transfusions, Sippy regime followed by liver diet later

J H Male, age 50 Diagnosis Ulcer of stomach, secondary anemia.

History Operation for ulcer four years before, hematemesis and melena 18 months ago, weakness for last two or three months, tarry stools for one week

Physical examination Pallor, right rectus scar, small mass just under anterior abdominal wall, no free HCl

March 31 Red blood cells 2,200,000, hemoglobin 35 per cent

April 2 Transfusion 600 cc

April 27 Red blood cells 4,000,000, hemoglobin 60 per cent

May 20 Red blood cells 3,900,000, hemoglobin 52 per cent

Course Gradual improvement on Sippy régime, one transfusion and iron injections

W S Male, age 49 Diagnosis Ulcer of duodenum, secondary anemia

History Attacks of gaseous eructations, flatulence and pain in epigastrium for twelve years Loss of strength and weight and tarry stools for 6 weeks

Physical examination Pallor, palpable liver, stool and stomach contents guaiac + + + +

April 8 Red blood cells 3,100,000, hemoglobin 55 per cent

May 6 Red blood cells 3,900,000, hemoglobin 44 per cent

Course Bleeding stopped and strength returned on Sippy diet

N B Male, age 50 Diagnosis Ulcer of the duodenum, secondary anemia

History Epigastric pain and loss of weight nine months before, gastrojejunostomy six months before with relief, Vomited fresh blood six hours before admission

Physical examination Pallor, low blood pressure April 23

May 17 Transfusion 500 cc

May 23 Red blood cells 3,100,000, hemoglobin 34 per cent

June 3 Transfusion 500 cc
 June 8 Transfusion 550 cc.
 June 10 Red blood cells 3,000,000, hemoglobin 40 per cent.
 June 27 Red blood cells 3,800,000, hemoglobin 60 per cent
 Course Continued bleeding until after third transfusion Steady recovery thereafter on Sippy régime. No liver

S D Female, age 36 Diagnosis Pernicious anemia.
 History Pallor for three years, dyspnea, numbness and tingling of hands for two years, four transfusions without improvement, circulatory failure, generalized edema and dyspnea for four weeks
 Physical examination Icteric pallor, generalized edema.
 June 3 Red blood cells 1,100,000, hemoglobin 20 per cent
 June 23 Red blood cells 1,170,000, hemoglobin 45 per cent.
 July 12 Red blood cells 2,200,000, hemoglobin 45 per cent
 Course Disappearance of edema, return of strength and color on Lilly's Liver Extract.

J J Male, age 48 Diagnosis Carcinoma with metastases following carcinoma of stomach, secondary anemia.

History Loss of appetite for three months, pallor, weakness, dyspnea and loss of 30 lbs for two months

Physical examination Icteric pallor, systolic murmur, large liver, absent deep reflexes

June 14 Red blood cells 680,000, hemoglobin 18 per cent
 June 16 Transfusion 450 cc.
 July 6 Red blood cells 1,700,000, hemoglobin 34 per cent.
 July 18 Red blood cells 2,400,000, hemoglobin 50 per cent
 Course Temporary improvement on one transfusion and liver extract

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THE SURFACE TENSION OF THE BLOOD SERUM IN HYPERTHYROIDISM

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The present communication is a report of an investigation of the surface tension of the blood serum in patients with severe thyroid intoxication. The general plan of the study has been as follows: Determinations of the surface tension were made upon samples of blood serum from untreated patients immediately upon admission to the hospital. Treatment with iodine (in the form of Lugol's solution) was then given in sufficient amount and over a sufficient period of time to allow an exhibition of its clinical effect, when the surface tension studies were repeated. Later the surface tension was again determined after surgical operation (double partial lobectomy of subtotal thyroidectomy) in order to observe any change resulting from the diminished activity of the thyroid gland due to its partial removal. In some cases iodine was continued for a short time after operation.

The direct reading tensiometer of Du Noüy (1) was used for making the surface tension determinations, and all the precautions recommended by him were carefully followed. The watch glasses used were of uniform size (diameter 8 cm.) and the same amount of serum, approximately 2 cc., used each time. The glassware used was boiled for two hours in a concentrated solution of sulphuric acid to which had been added 15 cc. saturated solution of potassium bichromate per liter. The watch glasses were washed not longer than two or three days before using and were flamed a short time before use in order to insure uniform spreading of the serum. The greatest care was taken throughout to avoid touching with the hands any glassware, including the collecting apparatus, centrifuge tubes and watch glasses.

The blood for the surface tension determinations was collected in

TABLE 1
Surface tension determinations

Subject	Date	Surface tension— serum			Remarks
		Initial read ing	Read ing after 2 hours	Drop	
Normal subjects					
		<i>dynes per sq cm</i>	<i>dynes per sq cm</i>	<i>dynes</i>	
E G N	November 18, 1925	56.6	49.6	7.0	Staff
	November 27, 1925	56.8	49.7	7.1	
	January 7, 1926	57.1	49.6	7.5	
	January 8, 1926	56.7	49.6	7.1	
G A H.	November 18, 1925	56.6	49.7	6.9	Staff
	November 27, 1925	56.6	49.6	7.0	Staff
E H.	November 18, 1925	56.8	49.4	7.4	Staff
	December 1, 1925	56.6	49.3	7.3	Staff
T G	November 18, 1925	57.1	49.8	7.3	Staff
A. S	January 15, 1926	57.1	49.7	7.4	Student
H P	January 15, 1926	56.8	49.8	7.0	Student
C W	January 20, 1926	57.1	49.5	7.6	Student
I T	January 20, 1926	56.9	49.3	7.6	Student
S W	January 20, 1926	56.9	49.3	7.6	Student
L W	January 20, 1926	57.5	49.3	8.2	Student
E T	January 20, 1926	57.2	49.1	8.1	Student
W S	January 22, 1926	57.0	49.1	7.9	Student
J B	February 2, 1926	56.8	49.9	6.9	Student
E C	February 2, 1926	57.7	49.8	7.9	Student
Miscellaneous conditions					
G C	November 10, 1925	57.6	49.8	7.8	Incipient menopause, psycho- neurosis
R C	November 10, 1925	57.1	49.4	7.7	Bronchial asthma, very mild re- action to ragweed and feathers
C T	November 10, 1925	56.6	49.5	7.1	Unexplained vertigo Diag- nosis disease of vestibularap- paratus following fracture of skull in 1921
F P	November 10, 1925	57.1	49.6	7.5	Pregnancy, second month (de- livery normal)
P L	January 27, 1926	56.5	49.5	7.0	Hysteria
	February 2, 1926	56.7	49.5	7.2	

TABLE 1—*Concluded*

Subject	Date	Surface tension— serum			Remarks
		Initial read ing	Read ing after 2 hours	Drop	
Miscellaneous conditions—continued					
		dynes per sq cm	dynes per sq cm	dynes	
F B	February 2, 1926	56.9	49.4	7.5	Palsy
R. S	January 14, 1926	57.5	49.5	8.0	Arthritis deformans
F Mc	January 14, 1926	57.0	49.9	7.1	Arthritis deformans
	January 21, 1926	57.1	49.9	7.2	Arthritis deformans
M M	December 24, 1925	56.9	49.2	7.7	Recovered coryza
G C	January 18, 1926	57.3	49.5	7.8	Convalescent pneumonia
C. J	January 14, 1926	56.7	49.6	7.1	Scleroderma
	January 27, 1926	56.6	49.4	7.2	Scleroderma
O N	January 22, 1926	57.0	48.8	8.2	Scleroderma

the morning after sixteen hours of complete fasting, by venapuncture without stasis. It was drawn directly into a 15 cc centrifuge tube through an L-shaped glass capillary tube ground to fit on a platinum needle. After clotting it was centrifuged and the serum was poured into a watch glass, stirred, and a reading immediately made. After the reading, the watch glass containing the serum was covered by an inverted Petri dish and allowed to stand undisturbed for two hours, when a second reading was made to ascertain the time drop. In order to avoid disturbing the serum while standing, the watch glasses were placed on a revolving table similar to that described by Du Nolly.

All readings were made between 23° and 24°C by placing the apparatus in a hood where the temperature could be regulated and air currents eliminated. A control reading of the surface tension of running tap water was made at the same time as that of the serum to be sure the instrument was accurately adjusted. Tap water was preferred to distilled water because of the extreme care needed for proper preparation of the latter. Undiluted serum was used because it required little handling and the chance of contamination was therefore

TABLE 2
Surface tension determinations in cases of hyperthyroid disease

Number	Subject Age Color Admission date	Date of determination	Surface tension—serum			Basal metabolic rate	Iodine therapy operation	Van den Bergh reaction— serum	(a) Clinical diagnosis (b) Surgical pathological report on material removed at operation
			Initial reading	Reading after 2 hours	Drop				
			<i>dynes per sq cm</i>						
1	Ada H. 35 C November 5	November 11, 1925	53 3 48 7	4 6			Died November 11, 1925	Scleræ jaundiced	(a) Hyperthyroidism and exophthalmic goiter Autopsy also showed endocarditis
2	Mary S 46 W November 9	November 12, 1925 December 10, 1925 January 11, 1926	54 9 48 9 54 6 48 9 56 0 49 3	6 0 5 7 6 7	+57 +45		Before Lugol's 14 days Lugol's Operation December 10	Not done	(a) Hyperthyroidism and adenoma of thyroid (b) Mixed foetal and colloid adenomata (toxic)
3	Susan B 47 W November 22	November 24, 1925 December 15, 1925	53 3 48 6 55 7 48 8	4 7 6 9	+23 +17		Before Lugol's Lugol's November 24 to December 5 Operation December 7	Scleræ jaun diced on admission	(a) Exophthalmic goiter (b) Exophthalmic hypertrophy of thyroid
4	Sue V 23 W December 2	December 14, 1925 January 11, 1926	54 7 48 8 54 2 48 8	5 9 5 4	+25 + 9		7 days Lugol's Lugol's December 7 to Janu ary 11 Operation December 24	Not done	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic hypertrophy of the thyroid
5	Wm. Z 36 W December 9	December 14, 1925 December 23, 1925 January 5, 1926	54 6 48 5 54 8 48 8 56 0 49 0	6 1 6 0 7 0	+34 +22 +22		Before Lugol's 9 days Lugol's Operation December 23	Not done	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter

6	Addie F	December 15 1925	56 6 50 0 6 6	+34	Lugol's October 15 to November 6	Not done	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
	55 C	December 15 1925	56 6 50 0 6 6	+34	Lugol's November 25 to December 11		
	December 11	December 24 1925	56 7 50 1 6 6	+18	Operation December 16		
7	Norma W	January 5 1926	54 1 48 8 5 3	+30	Before Lugol's	Not done	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
	22 W	January 12 1926	53 8 48 6 5 2	+14	Lugol's January 10 to January 21		
	December 30	February 3 1926	55 8 49 0 6 8		Operation January 23		
8	John R.	January 21 1926	55 4 48 6 6 8	+59	Before Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
	49 W	January 30 1926	55 4 48 5 6 9	+44	11 days Lugol's		
	January 18	March 5 1926	56 6 49 4 7 2	+3	Operation February 23		
9	Beulah W	January 16 1926	56 8 50 0 6 8	+16	Before Lugol's	Negative	(a) Hyperthyroidism
	22 W	January 29 1926	57 1 50 1 7 0	+5	Lugol's January 24 to January 30		
	January 14				No operation		
10	See S.	January 30 1926	55 4 48 3 6 6	+50	Before Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
	29 S	February 10 1926	55 7 48 9 6 8	+27	11 days Lugol's		
	January 26	February 24 1926	56 4 49 0 7 4		Operation February 12		
11	Ernest C.	February 3 1926	55 3 48 6 6 7	+38	Before Lugol's	Negative	(a) Hyperthyroidism
	55 W	March 3 1926	56 0 48 7 7 0	+13	30 days Lugol's		
	January 29				No operation		
12	Louise S.	February 16 1926	54 6 48 6 5 8	+45	Before Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
	22 W	February 27 1926	55 1 48 8 6 4	+28	11 days Lugol's		
	February 11	March 23, 1926	56 2 49 0 7 2	-5	20 days post-operative	ter operation developed post-operative myxedema	
13	Gustava B	February 22, 1926	54 6 48 6 6 0	+67	Before Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
	39 W	March 10 1926	55 0 46 6 6 4		Lugol's March 1 to March 23		
	February 17	March 24 1926	56 0 48 9 6 1	+17	Operation March 11		

TABLE 2—Continued

Number	Subject Age Color Admission date	Date of determination	Surface ten- sion—serum		Basal metabolic rate	Iodine therapy operation	Van den Bergh reaction— serum	(a) Clinical diagnosis (b) Surgical pathological report on material removed at operation
			Initial reading	Drop Reading after 2 hours				
14	Zona C 21 W March 2	March 15, 1926	55 649 2	6 4	+ 8	Before Lugol's No operation	Negative	(a) Hyperthyroidism
15	Joseph K. 38 W March 4	March 6, 1926 March 23, 1926 April 4, 1926	54 448 9 54 648 9 54 948 9	5 5 5 7 6 0	+73 +37 = 0	Before Lugol's 15 days Lugol's Operation March 24	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
16	Ambrose W 42 W March 5	March 8, 1926 March 14, 1926	54 349 1 55 049 3	5 2 5 7	+26	Before Lugol's Lugol's March 8 to March 14	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
17	Tollin T 41 W March 9	March 28, 1926 March 12, 1926 March 26, 1926 April 29, 1926	55 949 0 56 048 9 56 549 2 57 149 2	6 9 7 1 7 3 7 9	+14 +14 +28	Operation March 23 Before Lugol's Before Lugol's Operation April 16	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
18	Gertrude Z 19 W March 15	March 18, 1926 March 23, 1926	56 349 4 56 549 4	6 9 7 1	+34	Before Lugol's Lugol's March 18 to March 31	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Fetal and colloid adenoma of thyroid
20	Mary E 29 W March 19	April 14, 1926 March 23, 1926 April 8, 1926 January 5, 1926	56 649 3 56 348 9 56 248 7 56 849 4	7 3 7 4 7 5 7 6	= 0 +65 +31 - 8	Operation April 3 Before Lugol's 17 days Lugol's 9 months post-operative	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter

21	Martha S. 53 W March 30	April 20, 1926 May 6, 1926	54 448 8 5 6 54 848 8 6 0	+31 +10	11 day Lugol's 10 days post-operative	Negative	(a) Adenoma of thyroid (b) Adenoma mixed fetal and colloid
22	Edna A. 26 W April 12	April 6, 1926 May 4 1926 June 1 1926	52 947 4 5 5 53 347 9 5 4 54 648 6 6 0	+21 +21 +11	Before Lugol's 18 days Lugol's 8 days post-operative	18 units (direct) 12 units 1 unit	(a) Adenoma of thyroid (b) Mixed adenoma
23	Lillian C. 22 W April 13	April 14, 1926 May 6 1926 September 30 1926	53 648 7 4 9 54 148 8 5 3 56 549 5 7 0	+73 +44 +11	Before Lugol's 19 days Lugol's 4 months post-operative	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
24	Anna B 18 W September 23	September 24, 1926 October 3 1926	55 949 8 6 1 56 349 7 6 6	+61 +37	Before Lugol's 7 days Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
25	Mary D. 27 W October 1	October 5 1926	54 748 8 5 9	+45	3 days Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter with one encapsulated adenoma
26	Minnie H. 21 C October 25	November 2 1926	55 149 0 6 1	+39	Before Lugol's No operation	Negative	(a) Hyperthyroidism
27	Wm. D. 38 W October 20	November 20 1926	56 449 0 7 4	+32	Before Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
28	Jeanie B 49 C November 2	November 4 1926 November 23 1926	53 749 5 4 2 54 349 4 5 1	+57 +37	Before Lugol's 13 days Lugol's	Trace Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
29	Henry B. 43 W November 15	November 16, 1926	54 349 5 4 8	+63	Treated before admission for blastomycosis probably with iodides	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
30	Wm. C. 22 C November 30	December 3 1926	53 648 8 4 8	+59	Before Lugol's	Trace	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter

TABLE 2—Continued

Number	Subject Age Color Admission date	Date of determination	Surface tension—serum		Basal metabolic rate	Iodine therapy operation	Van den Bergh reaction— serum	(a) Clinical diagnosis (b) Surgical pathological report on material removed at operation
			Initial reading	Drop Reading after 2 hours				
31	Margaret K 29 W July 6	July 11 1927	56 2 49 5	6 7	+54	Before Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
		July 19, 1927	56 6 49 6	7 0	+13	6 days Lugol's		
		July 31 1927	56 8 49 6	7 2		10 days post-operative		
32	Mable S 20 W July 13	July 19, 1927	54 3 48 8	5 5	+100 +101	Has received iodine 1 year before admission Died following operation	Negative	(a) Hyperthyroidism and toxic adenoma
33	Roxie M 29 W July 20	August 2, 1927	54 3 49 1	5 2		Before Lugol's	† unit Negative Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
		August 9, 1927	55 3 49 0	6 3	+23	19 days Lugol's		
		August 16, 1927	56 3 49 3	7 0	+22	12 days post-operative		
34	Effie D 37 C July 15	July 23 1927	55 8 49 4	6 4	+48	Before Lugol's	Negative	(a) Hyperthyroidism and toxic adenoma (b) Exophthalmic goiter
		August 4, 1927	56 7 49 7	6 9	+25	10 days Lugol's		
		August 19 1927	56 5 49 4	7 1	+19	10 days post-operative		
35	Elizabeth B 40 W July 23	July 30, 1927	54 8 48 8	6 0	+60	7 days Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
		August 9, 1927	55 0 48 9	6 1	+16	8 days post-operative		
36	Cornelia W 35 C July 19	July 23, 1927	56 3 49 2	7 1	+11	Before Lugol's	Negative	(a) Mild hyperthyroidism
		August 2 1927	56 8 49 4	7 4	+7	No operation		

37	Elmer S. 31 W July 25	July 27, 1927 August 2, 1927 August 23, 1927	54 2 49 0 54 1 48 8 54 2 49 0	5.2 5.3 5.2	+100 +51 -2	Before Lugol's 3 days Lugol's 10 days post-operative	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
38	May H. 27 W July 25	August 2, 1927	53 8 49 0	4.8	+60	Before Lugol's	Negative	
39	Alce K. 37 C July 26	July 27, 1927 August 9, 1927 August 19, 1927	53 7 49 3 54 0 49 2 54 6 49 1	4.4 4.8 5.5	+51 +23 +13	Before Lugol's 12 days Lugol's 9 days post-operative	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
40	Julia S. 42 W August 11	August 16, 1927 August 25, 1927 September 3, 1927	55 2 49 2 55 7 49 4 56 3 49 3	6.0 6.3 7.0	+46 +35 +34	Before Lugol's Before Lugol's 11 days Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
41	Ida A. 22 C August 11	August 13, 1927 August 22, 1927 August 31, 1927	56 3 49 8 56 9 49 7 57 4 49 9	6.5 7.3 7.5	+31 +4 +2	Before Lugol's 7 days Lugol's 7 days post-operative	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
42	Mildred P. 23 W July 23	July 26, 1926 August 6, 1927 August 29, 1927	54 3 48 8 55 0 48 9 55 4 49 3	5.5 5.9 6.0	+61 +13 -2	Before Lugol's 11 days Lugol's 21 days post-operative	Negative	(a) Hyperthyroidism and exophthalmic goiter (b) Exophthalmic goiter
43	Ella T. 42 C September 1	September 3, 1927	56 9 49 4	7.5	+61	Before Lugol's	Negative	(a) Adenoma of thyroid
44	Marie K. 35 W September 7	September 8, 1927	53 8 49 4	4.4	+58	Before Lugol's	Negative	(a) Hyperthyroidism and exophthalmic goiter

minimal Serum was also preferred to plasma because of the danger of hemolysis when an anti-coagulant was used Plasma was found to give a parallel but slightly higher reading than serum This was true in the case of oxalated blood and also when coagulation was prevented by a highly purified sample of heparin, kindly supplied to us by Dr W H Howell

The surface tension of the blood serum of forty-four patients suffering with hyperthyroidism was determined in the above way and, for comparison, that of fourteen normal individuals and twelve persons with miscellaneous conditions Table 1 gives the data obtained from the study of the controls, and table 2 the data obtained from that of the cases of thyroid intoxication

DISCUSSION

From table 1 it will be seen that the initial surface tension in the normal cases varied between 56.6 and 57.7 dynes, and the two-hour time drop varied between 6.9 and 8.2 dynes From table 2 it will be noted that thirty-nine out of forty-four cases of thyroid intoxication previous to treatment showed an initial surface tension reading of 56.5 dynes or less and that the time drop in thirty-eight of these cases was less than the minimal drop in the normal controls These relationships are shown graphically in chart 1

We consider that this data furnishes substantial evidence that during the period of thyroid intoxication a surface active substance is usually if not invariably present in the blood serum. Such a lowering of the surface tension in thyroid disease could be accounted for by the presence of bile acids in the serum Since no convenient method was available at the time for the estimation of the bile salts the Van den Bergh reaction was carried out in all but seven of the cases to serve as an indirect indication of the presence of bile Of the thirty-seven cases thus studied an amount of bilirubin above the normal limits, a "positive" Van den Bergh reaction, was found in the serum of four Two of the cases with a "positive" Van den Bergh showed no jaundice clinically and only a trace of bilirubin in the serum Serum from another case showed $\frac{1}{2}$ unit of bilirubin on admission but the Van den Bergh reaction was negative after nineteen days treatment with Lugol's solution Nevertheless the lowered surface tension



CHART 1 INDICATING THE INITIAL SURFACE TENSION READINGS AND THE TIME DROP IN CASES OF THYROID INTOXICATION TOGETHER WITH THE DETERMINATIONS MADE ON THE SERUM OF THE SAME PATIENTS AFTER IODINE TREATMENT AND AFTER SURGICAL OPERATION

The cross hatching represents the initial reading, the solid black represents the drop in surface tension in the same serum at the end of two hours.

A, normal subjects Cases of hyperthyroidism B, before treatment, C, after receiving Lugol's solution, D, after surgical operation

of the serum still persisted at this time. Of the seven cases in which the Van den Bergh reaction was not made, two showed slight icteric discoloration of the sclerae on admission which had cleared up at the time that the surface tension studies were made. The other five cases showed no clinical evidence of jaundice. All of these observations are indicated in table 2. Aside from these exceptions none of the cases showed either clinical evidence of jaundice or an abnormal amount of bilirubin in the blood serum as indicated by the Van den Bergh reaction.

We have considered the possibility that the surface active substance which appears to be present may be an unsaturated compound, possibly an unsaturated fatty acid. This aspect is further dealt with in the following paper (4). Under such circumstances the administration of iodine, even in the rather small amounts of Lugol's solution which are effective therapeutically, might be sufficient to neutralize its effect. However, the fact that iodine administration has not markedly altered the low surface tension of the serum in this condition appears to indicate that such is not the explanation of its action. After partial thyroidectomy it also appears that the return of the surface tension of the serum to normal is very slow.

No previous report has been found of a lowering of the surface tension of the blood serum in thyroid disease. Adlersburg and Sugar (2) state that the surface tension of the urine is lowered in Basedow's Disease. While the present study was in progress a paper by Wilhelmj and Fleisher (3) appeared, in which they reported that after thyroidectomy in guinea pigs a gradual rise in the surface tension of the plasma occurred, so that in nineteen to twenty-two days the readings were definitely abnormal. They find that the time drop, after twenty minutes, was in general less in the plasma from the animals operated upon than in the plasma from normal controls. Essentially the same differences were found by them when readings were made after two hours as were found after an interval of twenty minutes. These authors also made a study of the effect of thyroxin and thyroid extract administration to guinea pigs. In most cases a definite decrease in the surface tension of the plasma was found, but little change on the average was detected in the time drop.

CONCLUSIONS

1 The surface tension of the blood serum is lower than normal in many cases of thyroid intoxication. This is associated with a diminished time drop at the end of two hours, when compared with that present in the serum of normal persons.

2 The administration of iodine in the form of Lugol's solution has an appreciable effect in increasing the lowered surface tension.

3 After operation involving the partial removal of the thyroid gland there is a tendency for the surface tension of the serum to rise even more than after iodine.

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THE PLASMA FATS AND THE IODINE ABSORPTION CAPACITY OF THE FATTY ACIDS IN HYPERTHYROIDISM

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A diminution in the surface tension of the blood serum has been found in many cases of hyperthyroidism as reported in a previous paper (1). Since it is well known that the unsaturated fatty acids are highly surface active, we have investigated the amount of these substances in relation to the plasma fats as a possible cause of the above observed phenomenon in patients with this disease. The blood fats in a short series of normal persons studied at the same time as a basis for comparison.

Sixteen cases of hyperthyroidism and exophthalmic goitre have been studied. The blood was collected shortly after the patient was admitted to the ward and before the administration of iodine was commenced. Determinations were again made when the therapeutic effect of the iodine administered was considered to be at its maximum, and still later after surgical operation.

Iodine was administered in the form of Lugol's solution, the usual dosage being 30 minims daily. In many cases the administration of Lugol's solution was continued for a short period after operation in dosage of 5 to 10 minims daily. The patients were given no food for at least sixteen hours before collection of the blood for study. The basal metabolic rate was determined when possible the same day that the blood was taken, and also at frequent intervals thereafter.

Extensive studies have been made by Bloor, Leathes, Czonka and others (3, 4, 5) upon the fatty acids of normal blood plasma. The methods which we have employed in the studies here reported are as follows:

METHODS OF ANALYSIS

The total fats were determined in oxalated plasma or serum by the titrimetric method of Stewart and White (6) which was modified as follows. The plasma (5 to 8 cc) was measured into about 18 volumes of a 3:1 alcohol-ether mixture drop by drop, and heated to boiling in a hot water bath with rotation. It was then cooled, filtered, and made up to a definite volume with the alcohol-ether mixture, including the washings of the protein coagulum on the filter. Aliquots of the extract, in duplicate, representing 1 to 2 cc of the plasma were placed into 60 cc Florence flasks of pyrex or Nonsol glass. Five cubic centimeters of $N/10$ NaOH were added from a calibrated pipette or micro-burette, and the mixture slowly saponified on a moderately hot steam bath for about 2 hours until almost dry. It was found that at this point saponification of the neutral fats was not invariably complete as is claimed by the authors of this method. However, in every case complete saponification was effected by the addition of 5 cc of absolute alcohol, with subsequent boiling and continued evaporation on the steam bath for a further period of an hour or more. The fatty acids of the soaps were now liberated by the addition of accurately measured 5 cc $N/10$ HCl. The contents of the flask were boiled down on a free flame to about 1 cc, 10 cc of absolute alcohol and two drops of a 0.5 per cent phenolphthalein in 50 per cent alcohol were added, and the solution brought to boiling. The final titration with carbon dioxide free $N/10$ NaOH was then carried out with a burette graduated in 0.02 cc divisions and provided with a fine tip. The titration was carried on to a light pink color which persisted for at least one minute. Each set of determinations was accompanied by two or three blank determinations on the reagents alone, and the blank figures were subtracted from the final titration. Frequent checks with solutions of pure tripalmitin, triolein and tributyrin, and with mixtures of these fatty acids were performed, and these determinations convinced us that the simple method as outlined above yielded results which were accurate within 5 per cent of the theoretical values. The chief advantages of this modification over the original method are in the certainty of more complete saponification of the fat, in the use of larger samples of material and in obviating the use of the Rehberg microburette which is difficult to obtain and to manipulate. By this method the analyses yield figures which include the free fatty acids, and the acids combined in the neutral fats, soaps, cholesterol esters and in the phosphatids. The figures for total fat given in the tables were calculated in terms of tripalmitin and are therefore not strictly comparable with figures obtained by the use of other methods involving the weighing of the total soluble fat or by means of nephelometric comparison against an arbitrary standard of a mixture of fatty acids.

The iodine number of the fat was determined in the alcohol ether extracts by the admirable microadaptation of the well known Hanus method described by Gibson and Howard (7) and used by these authors for the determination of the iodine number of the blood fats in pernicious anemia. In tables 1 and 2 the iodine

figures are given in two columns. In the first column are shown the grams of iodine absorbed by 100 grams of fat.

Cholesterol determinations were made from the same alcohol-ether extract as the fats according to Sackett's (8) modification of Bloor's method for the determination of cholesterol in whole blood and serum.

The basal metabolic rate was determined by means of the Benedict Roth apparatus by the routine procedure employed in this hospital.

In table 1 are presented the results obtained for the total fatty acids, the iodine absorption and the iodine number in eleven normal individuals. In the group which was studied during a fasting period, the blood was collected before breakfast, at least 16 hours after the previous meal. In four of these the blood was collected both fasting and again $2\frac{1}{2}$ to 3 hours after a moderate lunch. The second group gives the figures for blood collected at various times after eating.

As will be observed, quite constant figures were obtained for the fasting state. The total fat of the plasma varied between 333 and 492 mgm. per cent, average 426 mgm. per cent. The iodine absorbed varied from 316 to 412 mgm per cent, average 351 mgm, while the iodine number of the fat varied between 66 and 104, average 84. Remarkable constancy was found for any given individual on whose blood analyses were repeated on different days. With the ingestion of ordinary mixed food it was found, as expected, that in 1 to $3\frac{1}{2}$ hours the concentration of the total fat of the blood had risen greatly to an average of 51 per cent above the fasting average. The iodine absorbed per 100 cc. plasma rose 23 per cent higher, while the iodine number (degree of unsaturation) of the fatty acids had fallen 18 per cent of the fasting average. This seems to indicate that the post-prandial increase in the blood fat is chiefly accounted for by the saturated fatty acids.

In table 2 are presented data upon sixteen patients in various stages of thyroid intoxication. Most of these, as far as could be determined, were not given any special treatment or medication before our study began. The exceptions are recorded in the last column under "Remarks." It will be noted that in 13 of these cases the initial plasma fat concentration is considerably lower than in the normal subjects, varying from 123 to 307 mgm. per cent. This low plasma fat is in every case associated with a high iodine number, but the

amount of iodine absorbed per 100 cc of plasma appears to be within our normal range. It seems, therefore, that the absolute concentra-

TABLE 1

Total fatty acid concentration (as tripalmitin) and iodine number in blood plasma from normal individuals

Subject	Date	Total fatty acids	Iodine absorbed	Iodine number	Remarks
Fasting					
		<i>grams tripalmitin per 100 cc plasma</i>	<i>grams per 100 cc plasma</i>		
E N	November 4	0 338	0 365	107	
	December 30	0 333	0 357	98	
	January 24	0 355	0 370	104*	
F B	December 30	0 487	0 327	67	
	January 31	0 492	0 341	69*	
L F	January 31	0 492	0 381	77*	
F H	January 31	0 369	0 316	86*	
H. C	February 12	0 446	0 408	92	
	January 16	0 458	0 412	90	
M G	January 31	0 338	0 327	97	
I W	January 31	0 492	0 326	66	
Average		0 426	0 351	84	Fasting
Not fasting					
E N	January 24	0 556	0 369	66	2 5 hours after moderate meal
F B	January 31	0 860	0 390	45	3 hours after moderate meal
I F	January 31	0 630	0 419	66	3 hours after heavy meal
F H	January 31	0 557	0 381	68	3 hours after heavy meal
W P	December 2	0 634	0 440	69	2 5 hours after light breakfast
T C	December 6	0 554	0 526	95	3 5 hours after light lunch
E B	December 2	0 846	0 622	73	1 2 hours after heavy meal
D D	December 6	0 492	0 365	74	1 hour after light lunch
Average		0 641	0 434	69 5	Non-fasting

*Repeated same day after taking food (see below in this table)

tion of the unsaturated fatty acids is not increased in these cases, and that both the lowering of the total fat and the high iodine number of the plasma fat are due to a deficit in the saturated fatty acid radicals

Under iodine therapy, with or without operation, the total plasma fat rises remarkably, often to a concentration much higher than that found in fasting normal subjects. That the rise in plasma fats under this treatment is due largely to an increase in the saturated rather than the unsaturated fats, is again shown by a sharp drop in the iodine number of the fat, while the absolute amount of iodine absorbed per 100 cc. plasma remains approximately constant or even rises in some cases. Jobling and Petersen (8), citing older literature, pointed out some years ago that the administration of iodides tends to saturate the unsaturated fatty acids and thus destroy their antitryptic property. If such saturation or oxidation of the unsaturated fatty acids occurred in our hyperthyroid cases, it must have taken place but to a slight extent, for the absolute amount of iodine absorbed per 100 cc. of plasma did not decrease. The increase in the total fatty acids in the circulating blood was, as pointed out above, due to an accretion of saturated fatty acids.

The cholesterol determinations indicated low values in the more severe cases of hyperthyroidism and a definite increase towards the normal or slightly above the normal range as symptoms improved. The increase appears to parallel the increase in the saturated fatty acids. Low figures for the blood cholesterol have been reported by Dennis (10) in four cases of severe hyperthyroidism and figures within normal limits in four mild cases. No consecutive figures throughout the course of the treatment were given, and no data are given upon which to judge of the severity of the disease or of the exact diagnosis. Epstein and Lande (11) published in 1922 an interesting series of figures showing an inverse relationship between the basal metabolic rate and the cholesterol level in the blood in certain conditions. Low cholesterol figures are reported in cases of exophthalmic goitre and toxic thyroid adenomas. On the other hand in a series of cases with subnormal basal metabolism, including myxedema and nephrosis, high blood cholesterol figures were found. Thyroid therapy in some of these latter cases as well as in two cases of nephrosis recently reported by Liu (12), resulted in a lowering of the blood cholesterol as the basal metabolic rate came down and the clinical symptoms improved.

TABLE 2
Fatty acid concentration and iodine number in hyperthyroidism

Number	Subject Age Color Date admitted to hospital	Date of determination	Iodine therapy operation	Total fatty acids		Iodine absorbed		Iodine number	Cholesterol	Basal metabolic rate	Remarks, surgical pathological report on gland material removed at operation
				grams triolimi lin per 100 cc plasma	grams triolimi lin per 100 cc plasma	grams per 100 cc plasma	grams per 100 cc plasma				
1	Mary E 37 W March 19, 1926	March 23	Before Lugol's 17 days Lugol's 9 months post-operative	0 258	0 337	0 337	155	130	155	+65	Exophthalmic goiter
		April 8		0 323	0 357	0 357	192	110	192	+31	
		January 15		0 400	0 325	0 325	256	81	256	- 8	
2	Martha S 53 W March 30, 1926	April 6	Before Lugol's 11 days Lugol's 10 days post-operative	0 307	0 369	0 369	121	121		+25	Clinical diagnosis hyperthyroidism Pathological report, adenoma of thyroid
		April 20		0 368	0 564	0 564	248	152	248	+31	
		May 6		0 574	0 503	0 503	226	87	226	+10	
3	Edna A. 46 W April 12, 1926	April 16	Before Lugol's 18 days Lugol's Operation	0 283	0 296	0 296	130	105	130	+21	Given iodine before admission Van den Bergh reaction 18 units direct April 16 12 units direct April 24 Toxic adenoma
		May 4		0 325	0 326	0 326	182	100	182		
		May 24									
4	Lillian C 22 W April 13, 1926	April 14	Before Lugol's 19 days Lugol's 4 months post-operative	0 301	0 343	0 343	122	114	122	+73	Given thyroid extract before ad- mission Exophthalmic goiter
		May 6		0 437	0 347	0 347	238	79	238	+44	
		September 30		0 530	0 323	0 323	204	61	204	+11	

5	Mary B 27 W October 1, 1926	October 5 October 27 November 17	Before Lugol's 25 days Lugol's 20 days Lugol's	0 502 0 529 0 661	0 345 0 355 0 532	69 67 80	118 130 246	+55 -12	Exophthalmic goiter
6	Minnie H. 23 W October 25, 1926	November 2 November 11	Before Lugol's 9 days Lugol's	0 269 0 554	0 357 0 485	133 87	135 207	+29 +14	Clinical diagnosis hyperthyroidism No operation
7	Jennie B 49 C November 2, 1926	November 4 November 23 December 16	Before Lugol's 13 days Lugol's 16 days post-operative	0 269 0 323 0 501	0 357 0 423 0 469	133 131 93	115 174 268	+57 +32 -18	Exophthalmic goiter
8	Henry B 45 W November 30, 1926	November 16 December 11 December 26	Before Lugol's 16 days Lugol's 13 days post-operative	0 538 0 545 0 572	0 421 0 423 0 572	78 77 89	200 223	+63 +43 +20	Treated before admission for blasto- mycosis probably with iodides Exophthalmic goiter
9	Wm. C. 22 C November 30	December 3 December 15 January 15	Before Lugol's 10 days Lugol's 18 days post-operative	0 123 0 345 0 538	0 272 0 353 0 425	221 102 79	66 213 254	+59 +41 -3	Exophthalmic goiter
10	Nancy G 21 W December 2, 1926	December 15 December 26 January 6	Before Lugol's 10 days Lugol's 9 days post-operative	0 303 0 396 0 563	0 381 0 376 0 445	126 95 79	142 252	+28 -2 -12	Exophthalmic goiter
11	Florence F 35 W December 4, 1926	December 5 December 28 January 15	Before Lugol's 22 days Lugol's 16 days post-operative	0 169 0 330 0 415	0 347 0 405 0 330	205 123 112	89 172 224	+33 -14	Exophthalmic goiter
12	Frank K. 31 W December 30, 1926	January 6 January 15 January 28	2 days Lugol's 10 days Lugol's 9 days Lugol's	0 431 0 569 0 557	0 354 0 364 0 410	78 64 72	238 286	+33 +3 +8	Exophthalmic goiter

TABLE 2—Continued

Number	Subject Age Color Date admitted to hospital	Date of determination	Iodine therapy operation	Total fatty acids		Iodine absorbed		Iodine number		Cholesterol		Basal metabolic rate	Remarks, surgical pathological report on gland material removed at operation
				grams triglycerids per 100 cc plasma	grams per 100 cc plasma	grams per 100 cc plasma	grams per 100 cc plasma			mgm per 100 cc plasma			
13	Lizzie J 46 C January 3, 1927	December 23	Before Lugol's	0 165	0 340	0 340	97	206					Exophthalmic goiter
		January 4	Before Lugol's	0 215	0 420	0 420	188	196				+70	
		January 29	19 days Lugol's	0 358	0 326	0 326	110	110				+27	
		February 15	16 days Lugol's	0 753	0 517	0 517	313	69				— 6	
14	Dolores I 23 W January 10, 1927	Jan. 12	Before Lugol's	0 276	0 306	0 306	172	112				+22	Exophthalmic goiter
		February 11	14 days post-operative	0 415	0 430	0 430	103	103				+ 6 + 1	
15	Bertha L 27 C January 28, 1927	January 12	Before Lugol's	0 246	0 345	0 345	113	140				+78	Exophthalmic goiter
		February	17 days Lugol's	0 340	0 368	0 368	210	108				+56	
		February 23	9 days post-operative	0 554	0 484	0 484	87	87					
16	Viola W 23 W January 7, 1927	January 31	Before Lugol's	0 307	0 404	0 404	181	131				+34	Exophthalmic goiter
		January 15	6 days Lugol's	0 415	0 345	0 345	83	83				+28	
		February 11	11 days post-operative	0 581	0 584	0 584	100	100					

These observations upon the fatty acids and cholesterol indicate that significant changes in fat metabolism occur under iodine therapy in cases of thyroid intoxication. In general the data in table 2 show that the increase in the blood fat accompanies the lowering in the basal metabolic rate and the clinical improvement. Beyond the fact that the surface tension of the blood serum is definitely lowered in hyperthyroid disease (1) there does not appear to be any obvious parallelism between it and the fat figures presented. The surface tension often remains low after iodine therapy even when the fats have returned to a normal level.

SUMMARY

Data are presented on the distribution of the fatty acids and their relative degree of unsaturation (iodine number) in the blood plasma of eleven normal individuals and in sixteen cases of hyperthyroid disease before and after iodine therapy.

The total fatty acids of the plasma are markedly decreased in the untreated cases and the iodine number of these acids is greatly increased. These changes appear to be due not to an increase in the unsaturated fatty acids but to a decrease in the saturated acids.

Under iodine treatment and after operation, coincident with the lowering of the basal metabolic rate, the total fat rises and the iodine number drops to normal because of an absolute increase in the saturated fat content of the plasma.

The cholesterol content of the plasma is low in the more severe cases of hyperthyroid intoxication. It rises with the increase of the saturated fatty acids as the clinical symptoms improve, and the basal metabolic rate returns to normal under iodine treatment and operation.

The writers wish to acknowledge the help of Miss Beulah Schaub in the determination of the basal metabolic rates.

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THE CARDIODYNAMIC CHANGES IN THE AORTA AND LEFT VENTRICLE DUE TO STENOSIS OF THE AORTA

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INTRODUCTION

Our understanding of the dynamic changes which occur in stenosis of the aorta is inadequate in certain respects. Part of the deficiency can be attributed to the inaccurate methods used in recording pressure curves. This can be obviated by using optically recording manometers of high efficiency, particularly if the aortic and left ventricular pressures are recorded simultaneously. Curiously enough such records are lacking.

An analysis of the optically recorded pressure curve of the left ventricle during varying stages of stenosis of the aorta also gives accurate information of the effect on contraction produced by prevention of ejection and shortening to various extents. When the aorta is stenosed, the ventricle contracts more nearly isometrically, the closest approach occurring when the stenosis is complete. Thus complete stenosis, especially if it be produced in the pulmonary artery, offers an opportunity of studying the isometric contraction of the mammalian ventricle, a subject that has been neglected.

An analysis of the optically recorded aortic pressure curve is important also because it may help to account for the sudden interruption in the central pulse, which Feil and Katz (1) have shown is the *anlage* of the anacrotic wave in the radial pulse. No evidence is available to indicate whether the characteristic changes in the optical records of the subclavian pulse of patients with aortic stenosis also occur in the aortic curve in experimental stenosis of the aorta.

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FIG 1 A CAST OF THE INTERIOR OF THE LEFT VENTRICLE AND AORTA OF A DOG MADE IMMEDIATELY AFTER DEATH (POSTERIOR VIEW) IS REPRODUCED TO SHOW THE LOCATION OF THE CONSTRICTION (INDICATED BY AN ARROW) AND ITS HOUR-GLASS SHAPE

We are indebted to Dr H Goldblatt for making the cast and to Prof T W Todd and his staff for the photograph

In the present report these matters will be discussed on the basis of optically recorded pressure curve simultaneously obtained from the aorta and left ventricle during various stages of stenosis of the aorta

METHODS

The pressure changes were registered by optically recording manometers (Wiggers and Baker (2)) using the double slit lamp of Katz and Baker (3) to avoid parallax between the two curves. The pressure in the two chambers at any given moment was thus recorded in exactly the same vertical plane. The dogs were anesthetized with morphine and sodium barbitol injected intravenously. The method of exposing the heart and inserting the manometers was the one customarily used in this laboratory. The various degrees of stenosis were produced by tightening a ligature around the aorta, using a specially designed screw arrangement for this purpose. The ligature was placed about 1 cm. or less above the free margin of the semilunar valves, the location being confirmed at autopsy. The constriction produced in this fashion was hour glass in shape, as can be seen in the photograph (fig 1, indicated by an arrow) of a plaster cast made immediately after the death of one of the animals. The aortic manometer was inserted through the left subclavian artery so that the end of its cannula was in the aorta about 1 cm. distal to the neck of the constriction.

The experiments were made under various conditions of arterial resistance, venous return and heart rate. The amount of alveolar CO_2 was maintained constant during each experiment. The vagi were cut in most cases, in a few, however, they were left intact.

RESULTS

The changes produced by stenosis of the aorta present a complicated picture because the effect of the primary changes are counterbalanced (or enhanced) by compensatory mechanisms. These compensatory mechanisms appear quickly and tend to persist as long as the stenosis is present. Experimental stenosis, as carried out in this research, increases the coronary flow and thus has little if any effect, provided the cardiac nutrition is adequate to start with. In several animals the effect of impairment in cardiac nutrition in this condition was determined by analyzing the changes which occur in the right ventricle when the pulmonary artery was stenosed, a stenosis in this location leads to a decrease in coronary flow.

The mechanical compensatory mechanisms are probably of the same nature in the acute experiments as in the clinical cases. The

short stretch of aorta between the valves and the constriction introduces no significant capacity factor which could prevent retention of blood within the ventricles

In other respects the experiments are different from the clinical condition of aortic stenosis. For example, ventricular hypertrophy, aortic insufficiency and myocardial involvement which usually complicate the clinical case are absent in these acute experiments. Our object was not to reproduce all the mechanisms which appear in clinical cases of aortic stenosis, but rather to evaluate the primary dynamic changes in stenosis of the aorta, to see how they are modified by concurrent changes which the associated increase in diastolic stretch produces, and to determine the further modifications which nutritional impairment might give rise to. Such an analytical method is a necessary step in obtaining a clearer idea of the manner in which the clinical picture is produced, but it is only the first step

A comparison of the changes in the left ventricular pressure curve with those occurring in the aortic

The fact that the aorta and left ventricle are in free communication during ejection would lead one to expect that during this period the contour of the aortic and left ventricular curves would be the same. The control curves (figs 2A, 3A and 6A), show such similarity during ejection, that is to say, from the time the pressure in the aorta begins to rise until the incisuric drop takes place. As a matter of fact, it became clear to us that when this similarity was not present in control records, for example, in segment A of figure 8, some artefact had been introduced depending on the placement of the ventricular cannula opening (Wiggers (4)). Such ventricular curves were discarded in this analysis.

When the aorta was stenosed the similarity of the curves during the ejection phase disappeared, the disparity increasing as the stenosis was increased, compare, for example, the portion of the pressure curves between the rise of the aortic pressure and the incisura in segments B, C, with the corresponding portion of the curves in segments A of figures 2, 3 and 6. It will be seen that although the amplitude of the aortic curve decreases, the amplitude of the ventricular curve increases, and that although the gradient of the rise of

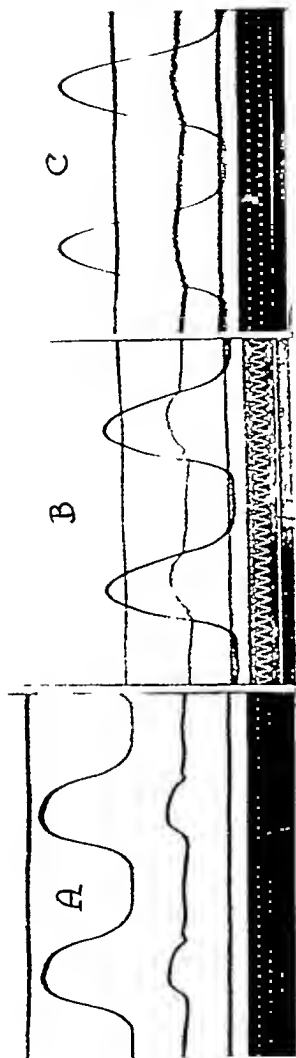


FIG. 2 SEGMENTS OF ORIGINAL RECORDS (REDUCED 1) ARE REPRODUCED TO SHOW THE EFFECT OF STENOSIS

Segment 1 is the control, *B* shows the effect of moderate stenosis, *C*, that of marked stenosis. In the interval between taking records 1 and *B*, the ventricular manometer mirror and base line mirror were shifted, without altering the relation between the two, to allow the entire ventricular pressure curve to be recorded in the latter. The upper curve in *A* is the ventricular pressure curve, the lower, the aortic. In *B* and *C*, the aortic curve intersects the ventricular. Time each double vibration equals 0.02 of a second.

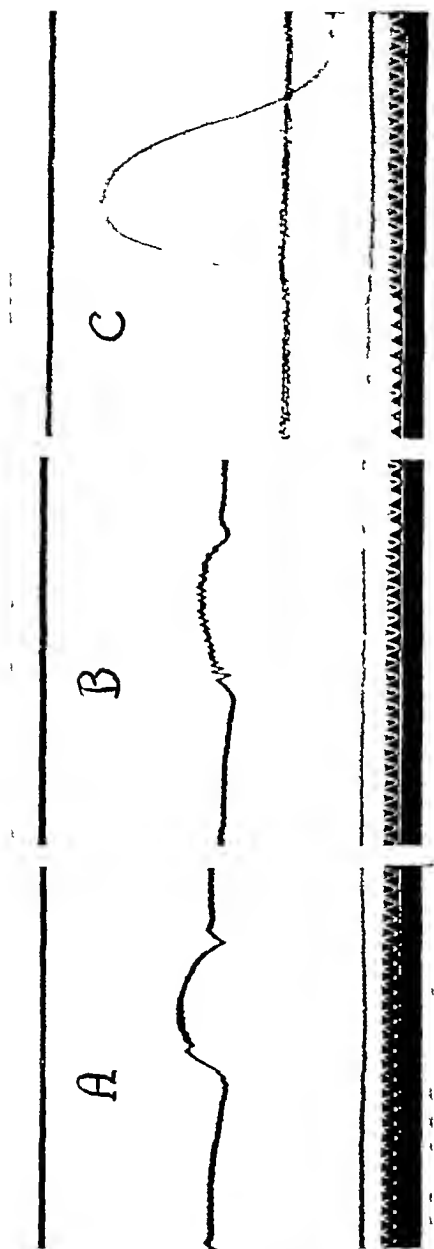


FIG. 3 SEGMENTS OF ORIGINAL RECORDS (REDUCED $\frac{1}{3}$) ARE REPRODUCED TO SHOW THE EFFECT OF STENOSIS. Segment *A* is the control, *B* shows the effect of moderate stenosis, *C*, that of complete stenosis. The upper curve is the aortic pressure, the lower, the intraventricular. Time each double vibration equals 0.02 of a second.

pressure in the aortic curve becomes more gradual, it becomes steeper in the ventricle. The location of the peak is also different in the two curves. The ventricular curve is free from the vibrations which appear during systole in the aortic curve, and there is no suggestion of a vibration equivalent to the anacrotic incisura present in the latter. These last two differences are not attributable to a less sensitive recording membrane on the ventricular manometer, as the difference in sensitivity of the two recording membranes was small and in several instances practically absent.³

The disappearance in the similarity of the basic form of the two pressure curves during ejection when the aorta is stenosed arises from the fact that the two chambers are no longer in free communication while blood is being ejected. The steeper and larger rise in ventricular pressure during this period, and the slower and smaller rise in aortic pressure are due to the decrease in the rate of conversion of potential mechanical energy in the ventricle to kinetic energy of flow. The development of tension in the ventricle is thus facilitated while the stretch of the arterial wall beyond the constriction is retarded. When the stenosis is complete, as in segment *C* of figure 3, no external work is done, except for pumping blood through the coronary arteries, practically all the effort is static, that is to say, is used in raising the pressure in the ventricle and its contents to a certain level for a certain time period. In complete stenosis of the pulmonary artery, *all* the effort of the right ventricle is static in this sense, if the ventricular volume were known, the total mechanical energy, so liberated, could be calculated and its variation with altered diastolic stretch and nutritional condition estimated.

The detailed description of changes in the intraventricular pressure curve

Stenosis of the aorta (or pulmonary artery) caused an increase in the area enclosed beneath the pressure time curve of the left (or right) ventricle. This increase resulted from increasing the height of the curve, its duration and the steepness of the ascending and descending

³ The anacrotic jog present in the ventricular record of figure 8 *B* is an artefact which is more pronounced in the control record, segment *A*. It is, therefore, to be disregarded.

limbs These changes in contour are seen in figures 2 and 3, and in the superimposed curves of figure 4⁴

The maximum pressure attained by the ventricle increased progressively as the degree of stenosis was increased, reaching values of 250 to 325 mm of mercury in complete occlusion of the aorta, a three

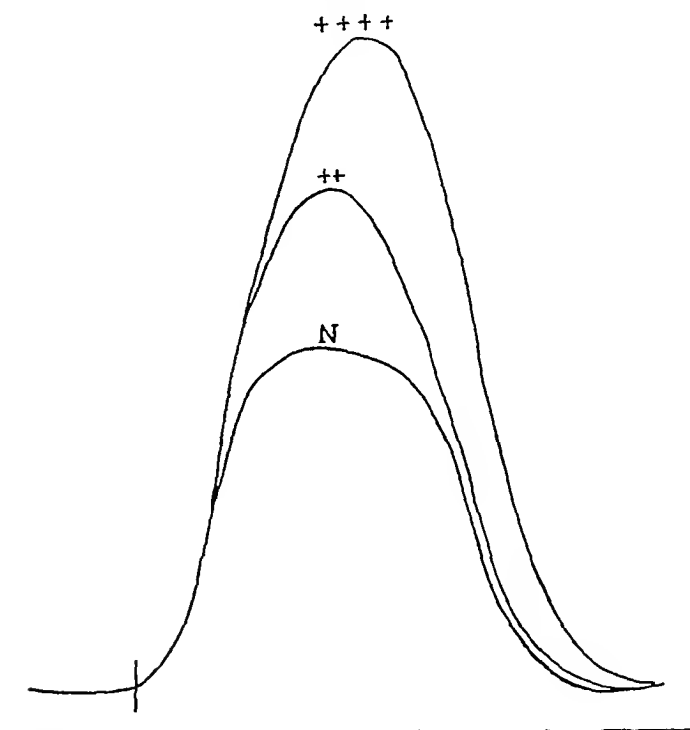


FIG 4 SUPERIMPOSED LEFT VENTRICULAR CURVES (ABOUT NATURAL SIZE) ARE REPRODUCED TO SHOW THE EFFECT OF STENOSIS OF THE AORTA ON THE PRESSURE CHANGES IN THIS CHAMBER

The curves are superimposed at the onset of the pressure rise, ignoring differences in initial tension. *N* is the normal record, ++ and +++, two stages of stenosis of the aorta. The details are described in the text.

to five-fold augmentation above control values (fig 3*A* and *C* and fig 6*A* and *D*). These changes agree very closely with those described by de Heer (5).

⁴ The use of a magnifying lens is advised to make the changes in gradient more distinct.

The rounded arch-shaped summit of the normal pressure curve disappeared and was replaced by a summit which progressively became more peaked as the contraction of the ventricle became more isometric. The time at which the peak was reached was variable. The progressively later occurrence of the peak, which de Heer's (5) curves show, and which might lead to the belief that its position in the ventricular curve was the same as in the aortic, did not occur in most of our records. In many cases the relation of the peak to the rise of pressure remained unchanged, in others (fig 6), it occurred earlier. Occasionally it shifted in one and then in the other direction in the same experiment as the degree of stenosis was augmented. Its location is doubtlessly dependent on the manner in which the contraction and relaxation processes in different fractions of the ventricle summate.

The usual effect of the stenosis was to prolong the duration of the curve (figs 2, 3 and 4). A similar difference in duration was noted by Fulton (6), between skeletal muscle allowed to shorten and the same muscle contracting isometrically. While Fulton could ascribe this change in his experiments to the prevention of shortening in our experiments it might be due to the increase in initial tension (Wiggers and Katz (7), and Wiggers (8)), which accompanies the stenosis (fig 3). The increase in initial tension (or diastolic stretch) was always present. This agrees with the observation of Straub (9) and with the finding of an increase in the diastolic volume by Straub (9) and de Heer (5) in similar types of stenosis. The inability of Lüderitz (10) and de Heer (5) to note an increase in initial tension can be ascribed to their failure to record a base line.

In mild stenosis the change in initial tension may be so small as not to be readily measurable. The changes were made more distinct by accurately retracing the curves on coördinate paper, after magnifying them four fold in a reflectoscope, so that their base lines coincided.

That the increase in diastolic stretch is not the sole cause for the prolongation of the curve is shown in continuous records taken immediately after the stenosis was made. A prolongation of the curve was present in the beat following the production of stenosis before any appreciable increase in diastolic stretch occurred.

The interaction of the primary effect of stenosis and of the associated change in diastolic stretch may be made clearer by describing a typical

experiment (fig 5) In this figure the normal pressure curve of the right ventricle (*N*) and the first and second beat (*1* and *2*) following immediately after the production of stenosis in the pulmonary artery, are superimposed (Beats *L* and *SL* will be referred to later) The curves are superimposed at the onset of the pressure rise so that their

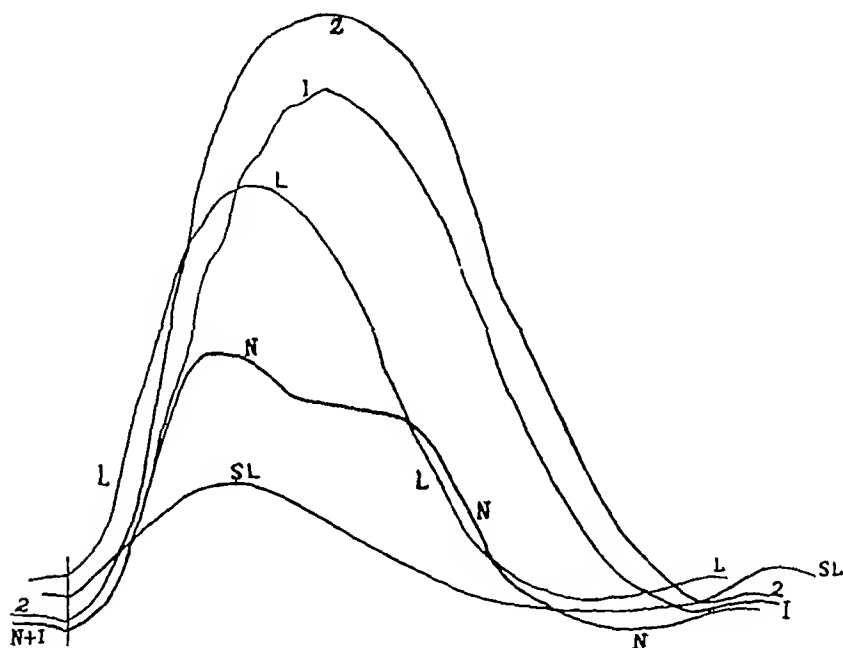


FIG 5 SUPERIMPOSED SUCCESSIVE RIGHT VENTRICULAR PRESSURE CURVES (ABOUT $1\frac{1}{2}$ NATURAL SIZE) ARE REPRODUCED TO SHOW THE EFFECT OF COMPLETE PULMONARY STENOSIS

The curves are superimposed at the onset of the pressure rise so their base lines coincide *N* is the control, *1*, the curve of a cycle during the systole of which complete stenosis was made, *2*, next beat, *L*, about the twentieth beat following, *SL*, about the thirty-fifth beat The details are described in the text

base lines coincide The stenosis in this particular case was complete and was made quickly *during the systole* of beat 1, as shown by the oscillation on the ascent of this curve The pressure immediately rises to a higher level, the summit becomes peaked, and the duration of the curve increases, and yet the initial tension is the same as before

(compare beats *N* and *I*) Such experiments show that the introduction of isometric conditions in itself increases the height of the curve, prolongs it and makes it more peaked. The rise of initial tension which occurs soon after (compare beats *I* and *2*) augments these changes.

Both of these curves (*I* and *2*) show the contour of a completely isometric contraction (or as nearly isometric as possible) in the mammalian ventricle, as compared with the normal after-loaded contraction (*N*). A comparison of the two beats (*I* and *2*) shows further that an increase in the initial tension of the ventricle causes an increase in the energy output in an isometrically contracting heart—a relation also true of isometrically contracting skeletal muscle. This is indicated by the increase in the area beneath the pressure time curve of the ventricle, which occurs in spite of the larger volume of the heart.

The continued presence of stenosis leads in this experiment to diminution in coronary flow and consequent impairment of nutrition. The initial tension rises still more in the beats following beat *2*, but because of the impairment in nutrition, the curves become smaller in height and shorter in duration, although still showing the characteristic peaked contour, for example beat *L*, which is about the twentieth beat after the appearance of stenosis. Finally, as the impairment in nutrition continues, the amplitude and duration become less than normal, for example beat *SZ* which is about the thirty-fifth beat after the appearance of stenosis. At this time the initial tension also becomes lower. Similar changes, attributable to nutritional impairment were noted in the other experiments made on the right heart.

Occasionally similar nutritional effects occurred in the left ventricle after complete aortic stenoses had been made and released several times in the same animal before beginning the experiment. Figure 6 is an example of such an experiment. The diastolic pressure was very low in this animal, the dilation of the ventricles persisted after the stenosis (the fifth one made) was released, and in a few minutes the heart ceased contracting. Although the height and contour changes of the ventricular curve are typical, its duration is not prolonged but abbreviated by the stenosis. This substantiates the fact emphasized previously by one of us (L N K (11)) that occasionally one effect of failure is an abbreviation of the contraction time of the heart.

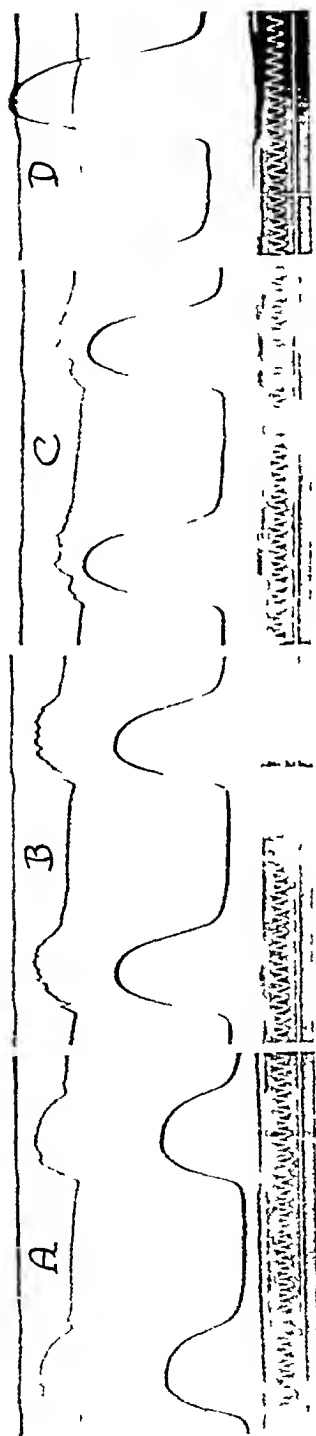


FIG 6 SEGMENTS OF ORIGINAL RECORDS (REDUCED $\frac{1}{3}$) ARE REPRODUCED TO SHOW THE EFFECT OF STENOSIS IN A POORLY NOURISHED HEART

Segment *A* is the control, *B* represents moderate, *C*, more marked, *D*, almost complete stenosis. The upper curve is the aortic pressure, lower, the left intraventricular pressure. Time each double vibration equals 0.02 of a second.

The detailed description of changes in the contour of the aortic pressure curve

A Pressure levels Before discussing the more significant changes in contour it is well to summarize the changes observed in the pressure levels in the aorta following stenosis. This summary is based on an analysis of the calibrated optically recorded aortic pressure records.

In agreement with previous investigators, we found that the diastolic pressure fell in most instances. The fall was particularly noticeable in the beats immediately after the induction of stenosis but was present in later beats also (figs 2, 3, 6 and 7). In a few cases of mild stenosis, however, we found in agreement with Lüderitz (10), that a rise occurred, or the level did not change. The systolic pressure also fell, as a rule more markedly than the diastolic, so that the pulse pressure also decreased (figs 2, 3, 6 and 7). In a few cases with mild stenosis and vigorous heart action, a temporary slight rise in systolic pressure and pulse pressure was present (fig 8). The mean blood pressure was not measured directly, but the changes in the other pressures indicate that it usually fell. This is in accord with the direct observations of MacCallum (12), de Heer (5) and Straub (9).

The lowering of the aortic pressure levels and the decrease in pulse pressure is due to the diminution in systolic discharge and minute output of the heart, a decrease noted by de Heer (5) and Straub (9). The cause is obviously the utilization of more of the mechanical energy of the ventricle to overcome the added obstructions caused by the stenosis, consequently less is left for kinetic energy of flow.⁵

Two compensatory mechanisms come into operation at once however. In the first place, the fall in aortic pressure reduces the augmented resistance against which the heart works and so allows utilization of more mechanical energy for kinetic energy of flow. In the second place, the retention of blood in the ventricle, by virtue of the resulting increase in diastole stretch, causes an augmentation in the chemical energy exchange, shown by an increased O_2 consumption, (Starling and Visscher (13)). The total amount of available mechani-

⁵ The effect of a reduced return of blood to the left ventricle might be an added factor in the clinical case. The increase in coronary flow which accompanies the diminution in peripheral flow would minimize such an effect in these experiments.

cal energy is thereby increased, assuming of course that the efficiency of the transformation is practically unchanged. In mild stenosis the effect of the increase in diastolic stretch may be large enough to counterbalance the primary effect of the constriction and cause a temporary rise in the pressure levels.

B The basic form and the superimposed finer changes Stenosis not only causes a lowering of the pressure levels in the aorta but also alters the fundamental form of the pressure-time curve. This consists in the ascent becoming more gradual and protracted and in the occurrence of the peak later in systole. Certain finer modifications also appear, namely, fine systolic vibrations preceded by a large decisive downward vibration, located on the early portion of the ascending limb of the curve. The incisura at the end of ejection, becomes less marked, and its obscurity is often increased by vibrations. The small after-vibration, which usually follows the incisura in the normal curve, tends to disappear. These changes are seen in figures 2, 3, 6, 7 and 8.

The presence of these changes in the aortic curve, which resemble those optically recorded in the subclavian pulse of clinical cases of aortic stenosis, precludes the idea that they arise in transmission from the aorta to the subclavian artery. They are absent from the ventricular pressure curve and so must arise *de novo* at or just beyond the constriction.

All of the changes become more noticeable, up to a certain point, as the stenosis is increased. The decline in the gradient of the ascent, for example, progressively becomes more noticeable (figs 2, 6 and 7), in mild stenoses, where the systolic pressure rises, a steeper ascent is seen occasionally (fig 8). The peak of the curve is another example, it tends to occur progressively later as the ascent becomes more gradual.

C The systolic vibrations These vibrations appear in the mildest grades of stenosis, even when the pulse amplitude is increased (fig 8). In fact, they may be larger in such cases than in more marked stenosis. The vibrations are irregular in size and frequency (fig 8 *B* and fig 7 *D*). The vibration frequency in this series ranged from 55 to 200 double vibrations per second, the range being somewhat less in a single beat. The vibrations do not coincide with the onset of ejection but appear after an interval of 0.02 to 0.04 of a second (figs 2, 3, 6, 7 and 8).

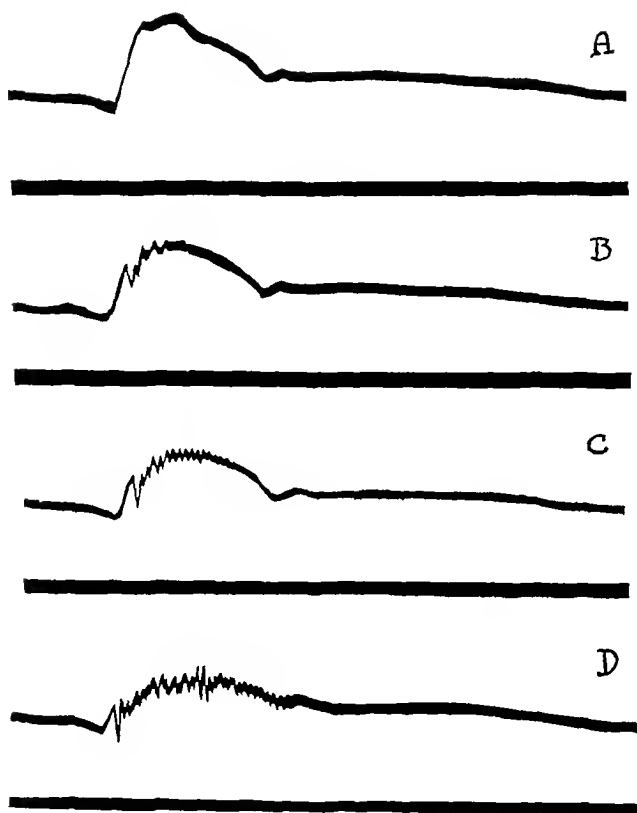


FIG 7 FOUR SEGMENTS OF AORTIC PRESSURE CURVES (ABOUT NATURAL SIZE) ARE PRESENTED TO SHOW THE CHANGES IN CONTOUR AT VARIOUS DEGREES OF STENOSIS OF THE AORTA

Segment *A* is a normal record segments *B*, *C*, *D*, successive increases in stenosis of the aorta from mild to fairly marked

They sometimes end before the incisura, but often are visible in early diastole (fig 8 *C* and fig 7 *D*) The duration of the vibration increases as the stenosis becomes more marked (figs 7 and 8) The vibrations found in these animal experiments resemble those observed by Feil and Katz (1), as to the time of their appearance, their vibration frequency and their irregularity

The manner in which these records were obtained precludes entertaining the idea that the delay in their onset and their persistence into diastole are due to differences in the rate at which the various

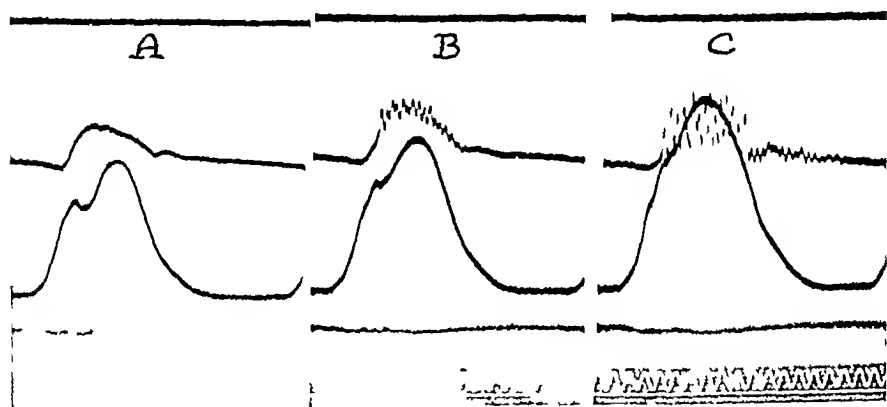


FIG 8 THREE SEGMENTS OF ORIGINAL CURVES (ABOUT $\frac{1}{2}$ NORMAL SIZE) ARE PRESENTED TO SHOW THE EFFECT OF MILD STENOSIS OF THE AORTA

Segment *A* is a normal record, segments *B* and *C*, two mild stages of stenosis. The upper curve is aortic pressure, the vibrations are enhanced by resonance effect. The lower curve is left ventricular pressure, the wave on the ascending limb is an artefact, as is also the summit which follows. This is indicated by the fact that in the normal curve (segment *A*) the contour of the ventricular curve does not resemble that of the aorta. Time each double vibration equals 0.02 of a second.

types of pressure changes are transmitted to the recording membrane, inasmuch as the entire liquid recording medium was encased in a rigid tube and the distance from the stenosis to the rubber membrane was approximately 15 cm. The sensitivity of the membrane which is relatively low for such a purpose, however, tends to diminish the amplitude of the vibrations, so that in certain cases, as in segments *B* and *C* of figure 2, they are barely discernible. In some cases, on the

other hand, as in segments *B* and *C* of figure 8, resonance effects probably increase their amplitude. The vibration frequency of these manometers (about 200 double vibrations per second) tends furthermore, to distort the vibrations somewhat. The properties of the recording membrane employed, however, do not introduce any appreciable delay in their registration (Broemser (14))

The vibrations are due to eddies and consequently more or less harmonic vibrations, produced by the axial stream flowing beyond the constriction. Their amplitude and vibration frequency are determined by the degree of the hour-glass distortion of the arterial wall, by the velocity with which blood flows past the constriction, and by the physical properties of the blood-filled elastic tube beyond. The delay in their onset is due to the inertia of the arterial system. This may also account in part for their persistence after ejection has ceased. The persistence may also be due to a backward movement of blood, which occurs during protodiastole (Frank (15)). While such explanations may account for the vibrations occurring immediately after ejection, they cannot explain those which appear later (fig 8 *C*). The latter may be the result of the rapid emptying of the aorta proximal to the constriction after the semilunar valves are closed. It is evident that when ejection terminates the pressure in this portion must be considerably higher than in the rest of the aorta.

D The sharp vibration on the ascending limb The sharp vibration which is characteristic of stenosis, appears even in mild stenosis (fig 8 *B*), but is more distinct in moderate stenosis (figs 2 *B*, 3 *B*, and 6 *B* and fig 7 *B*, *C*, *D*). In more marked stenosis it again becomes less distinct (figs 2 *C* and 6 *C*). The vibration usually appears as a steep downward incisura followed by an equally steep rise, on rare occasions, in mild stenosis, it may start with a component directed upward (fig 8). The normal aortic pressure curve is free of such a sharp vibration although occasionally, as in segment *A* of figure 3, a slight vibration may be seen. This, when it occurs, is always close to the maximum pressure level in the aorta, whereas the vibration in aortic stenosis always occurs on the ascending limb. The position of the vibration varies as the degree of stenosis is changed. The changes which occur in the vibration during the early stages of stenosis can be followed best by analyzing the records shown in figure 7. It

will be seen that as the stenosis increases, the ascent preceding the vibration becomes less steep, its duration decreases and its height diminishes. In other words the vibration occurs progressively earlier and lower down on the limb as the stenosis becomes more marked. Actual computations based on fourfold magnification of these curves show that the level at which the vibration starts is 75 per cent lower in segment *C* than in *B*, and 60 per cent lower in *D* than in *C*. In segment *B* it starts 0.02 of a second after the onset of ejection, whereas in *C* and *D* it starts sooner, namely 0.016 and 0.011 of a second after the onset of ejection, respectively. The vibration, at the same time becomes larger, has steeper gradients and a slightly shorter duration, that is to say, its duration in segment *B* is 0.010 of a second, in *C*, 0.009 and in *D*, 0.008 of a second.

The fact that this vibration has a steeper gradient than the ascent preceding it, excludes the possibility of its being a reflected wave from the constriction or any other point. It must be a forced vibration, in the same sense that Frank (16) uses the term in calling the incisura of the normal pulse a forced vibration.

The "breaking of the wave front" hypothesis of Bramwell (17) to which he attributes certain anacrotic vibrations, cannot be the cause in aortic stenosis, as the wave front is less steep than normally and consequently such a phenomenon could not possibly occur in the short distance of 1 cm. which separates the constriction from the opening of the manometer.

An explanation is offered which will rationally account for such a vibration. It is well-known that when a fluid stream is suddenly forced through a narrow opening into a larger tube, the stream becomes axial in the larger tube and tends to create a sudden sharp reduction in pressure in the marginal region. A similar phenomenon occurs in the aorta beyond the stenosis. The pull of this reduced pressure reacts on the wall of the aorta and sets up the vibration which we have described. Obviously the greater the velocity of the axial stream, the more marked will be the reduction in the marginal pressure and hence, the larger will be the vibration set up. Such an increase in the velocity of the axial stream accompanies the narrowing of the constriction.

This anacrotic vibration is the *anlage* of the anacrotic interruption in the radial pulse, just as the incisura is the *anlage* of the dicrotic wave.

TABLE 1

Effect of stenosis of the aorta on the duration of phases of cycle

Experiment number	Degree of stenosis	Duration of isometric contraction phase	Duration of ejection phase	Duration of total systole	Duration of preceding diastole	Duration of cycle
		<i>seconds</i>	<i>seconds</i>	<i>seconds</i>	<i>seconds</i>	<i>seconds</i>
70-1*	0	0 052	0 107	0 159	0 167	0 326
4	++	0 038	0 120	0 158	0 165	0 323
2	++++	0 038	0 140	0 178	0 142	0 320
70-21*	0	0 032	0 150	0 182	0 258	0 440
22	++	0 030	0 140	0 170	0 244	0 414
23	++++	0 023	0 132	0 155	0 235	0 390
74-1*	0	0 039	0 093	0 132	0 130	0 262
2	±	0 037	0 101	0 138	0 160	0 298
3	+	0 038	0 102	0 140	0 160	0 300
4	++	0 035	0 113	0 148	0 147	0 295
5	0	0 035	0 095	0 130	0 195	0 325
7	±	0 037	0 130	0 167	0 178	0 345
8	++	0 038	0 117	0 155	0 158	0 303
9	+++	0 038	0 122	0 160	0 163	0 323
74-24†	0	0 043	0 095	0 138	0 202	0 340
25	+	0 040	0 108	0 148	0 205	0 353
26	++	0 040	0 110	0 150	0 188	0 338
74-39‡	0	0 038	0 130	0 168	0 440	0 608
40	+	0 040	0 165	0 205	0 412	0 617
41	++	0 040	0 142	0 182	0 383	0 565
75-1†	0	0 050	0 090	0 140	0 145	0 285
2	+	0 048	0 095	0 143	0 145	0 288
3	++	0 053	0 095	0 148	0 143	0 291
5	+++	0 040	0 107	0 147	0 133	0 280
75-10†	0	0 028	0 124	0 152	0 370	0 522
12	+	0 030	0 130	0 160	0 370	0 530
13	++	0 032	0 133	0 165	0 380	0 545
15	++++	0 032	0 139	0 172	0 403	0 575
76-1†	0	0 058	0 168	0 226	0 215	0 441
3	++	0 055	0 200	0 255	0 168	0 423

* Vagi intact.

† Vagi cut.

‡ Vagi cut. During action of pilocarpin

TABLE 1—*Concluded*

Experiment number*	Degree of stenosis	Duration of isometric contraction phase	Duration of ejection phase	Duration of total systole	Duration of preceding diastole	Duration of cycle
		<i>seconds</i>	<i>seconds</i>	<i>seconds</i>	<i>seconds</i>	<i>seconds</i>
76-9†	0	0 042	0 160	0 202	0 215	0 417
11	++	0 035	0 190	0 225	0 180	0 405
80-1†	0	0 032	0 105	0 137	0 215	0 352
2	+	0 032	0 113	0 145	0 220	0 363
3	+++	0 040	0 130	0 170	0 193	0 363
80-5†	0	0 032	0 103	0 135	0 230	0 365
6	+	0 032	0 108	0 140	0 205	0 345
7	+++	0 032	0 130	0 162	0 195	0 357
80-17§						
Beat 2	0	0 023	0 100	0 123	0 205	0 328
Beat 4	+	0 023	0 100	0 123	0 200	0 323
Beat 6	++	0 030	0 103	0 133	0 192	0 325
Beat 9	+++	0 035	0 110	0 145	0 185	0 330

§ Vagi cut Consecutive beats in case of progressively increasing stenosis

The changes in duration of the phases of the cardiac cycle

In the course of this investigation a systematic analysis was made of the duration of the phases of systole and the changes in cycle length, with the idea of comparing them with changes observed in clinical cases. The data of typical experiments are given in table 1.

The results may be succinctly stated as follows. The cycle shortened slightly in most cases as the stenosis increased, regardless of whether the vagi were cut (last column). This is contrary to clinical experience. The abbreviation was not always present, in some cases practically no change occurred, (for example, in experiments 70, 1, 75, 1 to 5, 80, 17) in others a lengthening was noted (for example, in experiment 75, 10 to 15). The part played by such factors as reflexes, and by mechanical stimulation of nerves caused by the ligature cannot be ascertained at present.

Total systole^a lengthened, as a rule (column 5, table 1). On rare

^a Only those beats in which the end of ejection could be accurately determined were measured.

occasions when heart failure was imminent, it shortened (for example, in experiments 70, 21 to 23) The lengthening of total systole was due to an increased duration of ejection and often occurred in spite of an unchanged or even an abbreviated isometric contraction phase (columns 3, 4 and 5, table 1) The lengthening of ejection and total systole was most noticeable in marked degrees of stenosis. In mild stenosis it was sometimes absent (for example, in experiments 80, 17, beats 2 and 4) The changes in the systolic phases were similar to those noted in clinical cases (Katz and Feil (18)), except that the consistent lengthening of the isometric period was absent in the animal experiments They agree more closely with those made by Lüderitz (10) and by de Heer (5) on animals

The lengthening of systole and ejection is in part due to the increase in diastolic stretch (Wiggers and Katz (7)) accompanying the stenosis but probably also to the prevention of shortening (Fulton (6)) The slight changes in the isometric period are the result of the opposing action of the greater diastolic stretch and greater arterial resistance, the former tending to abbreviate and the latter to prolong this period (Katz and Feil (18))

SUMMARY

1 An analysis was made of the effects produced by stenosis of the aorta 1 cm above the free margin of the semilunar valves, based on optical pressure curves recorded simultaneously from the aorta and left ventricle

2 The condition thus produced allows a better opportunity to evaluate the primary effects of the stenosis and the immediate mechanical compensatory mechanisms than the clinical case

3 The contour of the left ventricular curve is altered by stenosis of the aorta Its height is increased and the summit becomes more peaked as the contraction becomes more isometric At the same time, its duration increases and the ascent and descent are steeper No fine vibrations are superimposed

4 The changes in the pressure curve are shown to be partly the result of the constriction itself which decreases the conversion of the potential mechanical energy to kinetic energy of flow and partly the result of the increase in the diastolic stretch of the ventricle

5 The effect of impairing the nutrition of the heart was analyzed by repeating the experiments on the right heart. This causes an abbreviation in duration and a decrease in the height of the pressure-time curve in spite of the opposing effect of the stenosis itself, and of the increased diastolic stretch.

6 The pressure curve of a completely isometric contraction of the right ventricle is reproduced.

7 The normal parallelism in the fundamental contour of the aortic and left ventricular curves during the ejection period disappears when a stenosis is created. The amplitude of the curves, as well as the gradients of the ascent, change in opposite directions, and the peaks no longer coincide in time.

8 The changes in the aortic pressure curve produced by the stenosis are summarized as follows:

- a Decreased pulse amplitude
- b Lowered level of the pressures
- c Prolongation of the ejection period
- d Diminished gradient of the ascent
- e Less decisive incisura with obscuring of its after-vibration
- f Superimposition of systolic (and early diastolic) vibrations on the curve
- g Appearance of a sharp vibration low down on the ascent of the curve

9 The resemblance of the aortic curve to optical curves recorded from the subclavian artery in clinical cases of aortic stenosis is evident.

10 The delay in the onset of the systolic vibrations, as well as their persistence into diastole, is pointed out.

11 The sharp vibration on the ascent, which changes its position with different degrees of stenosis, is analyzed and evidence is given to show that it is a forced vibration.

12 It is suggested that this vibration is created by the suction action of the suddenly produced swift axial stream beyond the constriction.

13 The importance of this vibration as the *anlage* of the anacrotic wave in the radial pulse is again emphasized.

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BLOOD VOLUME IN FEVER

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It has long been recognized that there are disturbances in water metabolism during fever, and increasing the water intake is now the most universally applied therapeutic measure used in controlling fever. The present study was undertaken to determine whether during fever there are fluctuations in blood volume that might be considered as reflections of the disturbed water metabolism.

In general, there is retention of water by the body as a whole during fever and release of this water again after defervescence. In 1869, the work of Leyden (1) demonstrated this as well as the increased heat production during fever. These facts have been rediscovered a number of times and gradually knowledge has emerged as to where the water retained during fever is stored. Water retention during primary pneumonia in children was demonstrated by weight charts (Lusky and Friedstein (2)). By means of an elastimeter water retention in the skin of ten cases of pneumonia in children was shown by Maver and Schwartz (3). Babies with fever excrete water given by mouth more slowly than normal babies (Hirsch (4)) and this seems to be due to actual water retention. Studies of scarlet fever show that the weight remains constant or that there is a slight gain in weight during the period of fever and this is accompanied by a positive chloride balance and dilution of the blood as measured by the serum protein concentration (Oppenheimer and Reiss (5)). During fever a gain in weight is accompanied by a lowering of the concentration of the serum protein but during convalescence there may be a gain in weight with a constant serum protein concentration. The authors interpreted the results to mean retention of water and salt during fever accompanied by a moderate blood dilution. Similar results were found in pneumonia (Sandelowsky (6)) except that in some of the

more severe cases, the author felt that part of the decrease in serum protein concentration was due to consumption of the proteins. Peabody (7) demonstrated a retention of chlorides, sodium and calcium and an increased excretion of phosphorus and magnesium during pneumonia. By analyses of the tissues, he came to the conclusion that the chloride retention could not be accounted for either by the pneumonic exudate or storage in increased concentration elsewhere and therefore was led to assume a generalized storage of water throughout the body. Thus previous studies of water metabolism seem to favor the view that during fever water and salts are retained diffusely throughout the body.

It is not known why water should be held in the body during fever. The retention of water and of salts are probably ultimately parts of the same process. Nitrogen split products may play a part in the holding of water. Cook (8) showed a rather sudden release of nitrogen products in the urine after the crisis in lobar pneumonia. This was shown not to originate from the exudate alone for it was more than could be accounted for in that manner. Whipple and Cooke (9) found a large increase in the urinary nitrogen output in dogs in which they had induced fever by sterile abscesses or by proteose intoxication. The increased nitrogen output comes with defervescence. Little is known of what part nitrogen split products play in the retention of water during fever, but they do not seem to play an important rôle since changes in the distribution of water between the tissues and blood may be brought about by conditions which do not lead to cell destruction.

Barbour (10) and his co-workers have studied the effects of warm and cold environments on the water content of the blood, serum and tissues of dogs. Exposure to cold resulted in a concentration of the blood and serum and an increase in the water content of the subcutaneous tissues and muscles. Warm environments, except those that are so warm as not to permit the body to maintain its normal temperature, dilute the blood and serum with water and salts. As this effect could be brought about by warming or cooling the brain alone, the workers felt that the changes were under the control of the central nervous system. Bancroft (11) and his co-workers found that warm environments lead to an increase in the blood volume of about 20 per

cent Thus the body seems to be able to shift water into or out of the blood stream by mechanisms involving no tissue injury

In the present paper the effect of fever on the blood volume was the chief subject of investigation In addition to the cases of typhoid fever, pyelitis, etc., a number of cases of primary pneumonia in children are used as examples of the effect of fever This raises the question of the effect of pulmonary insufficiency on blood volume and blood concentration True uncompensated deficiency of pulmonic function is rare An ideal example would be a state in which the circulation through the lungs was normal but oxygen was not readily absorbed and carbon dioxide not readily excreted Certain types of pulmonary edema approximate this condition The war gases produce an intense edema of the lungs, and accompanying this there is marked concentration of the hemoglobin (Underhill (12)) A similar concentration of the hemoglobin was found by Underhill and Ringer (13) in post-influenzal bronchopneumonia Excepting states of dehydration and shock, the concentration of the hemoglobin found by Underhill and Ringer is greater than is met in any other pathological state In ordinary lobar pneumonia, blood concentration does not occur and the changes seen need not be interpreted as caused by pulmonic deficiency The characteristic finding in pneumonia is that the venous and arterial blood have oxygen and carbon dioxide contents which differ from each other less than under normal conditions It is obvious that if the circulation is very rapid the arterial blood will not have time to lose its oxygen, the tissues will have no need to absorb all the oxygen offered by the rapidly circulating blood, and the blood may not have time to become saturated with oxygen in the lungs If there were difficulty in aerating the blood or in excreting carbon dioxide, one would find both an increased venous and arterial oxygen unsaturation, and the carbon dioxide would accumulate in the blood For the above reasons, rapid circulation seems to be the best explanation for the chief changes in the blood in pneumonia If this reasoning is correct, other fevers may produce similar changes and it seems justifiable to use primary pneumonia as an example of fever

The methods used in this investigation are the same as those used in the previous one (15) Blood volumes and chlorides were determined on twenty cases of primary pneumonia in children, seven cases

TABLE 1

Case	Date	Age yrs	Sex	Weight kg	Diagnosis	Fever	Blood volume— total			Blood volume per kilogram			Chlorides per 100 ml			Serum protein		
							Cell volume per cent	Blood ml	Plasma ml	Cells ml	Blood ml	Plasma ml	Cells ml	Blood mg	Plasma mg	Cells mg	Per cent	Grams
1	May 29, 1923	12	F	24 0	Typhoid	+	34 12,256	1,488	768	94 0	62 0	32 0						
1	May 30, 1923	12	F	24 5	Typhoid	+	33 02,130	1,427	703	186 6	57 8	28 7	499	576	342			
2	May 29, 1923	8	M	15 5	Typhoid	+	33 01,375	922	454	88 8	59 5	29 2	308	449	240			
2	June 15, 1923	8	M	16 2	Convalescent	0	36 31,027	654	373	63 4	40 4	23 0	466	516	377			
3	September 22, 1923	11	M	32 0	Typhoid	+	22 42,240	1,740	500	70 0	54 4	15 6	482	540	282			
4	June 18, 1923	5	F	16 3	Pyelitis	+	36 21,410	900	510	86 5	55 0	31 3	500	574	369			
5	June 28, 1923	6	F	20 0	Pyelitis	+	32 81,725	1,160	565	86,2	58 0	28 2	474	532	353			
6	July 27, 1923	7	F	17 0	Pyelitis	+	29 01,520	1,080	440	89 4	63 5	25 9	496	532	407			
7	September 14, 1923	8	M	23 4	Pyelitis	+	30 11,952	1,315	587	83 5	58 3	25 1	523	580	389			
8	July 19, 1923	9	F	21 5	Pyelitis	+	37 01,562	984	578	72 6	45 7	26 8	448	529	310			
9	January 1, 1923	10	F	28 4	Pyelitis	+	36 01,575	1,008	567	55 6	35 5	28 7	498	610	272			
10	July 4, 1923	10	F	29 0	Pyelitis	0	38 02,340	1,450	890	80 7	50 0	30 7	485	557	368			
11	May 16, 1923	10	M	27 3	Thoracic empyema	+	33 01,888	1,265	623	69 2	46 4	22 8	490	591	285			
12	May 23, 1923	12	F	34 5	"Influenza"	+	39 02,546	1,553	993	73 8	45 0	28 7	464	542	343			
13	May 26, 1923	4	M	14 0	Tuberculosis men- ingitis	+	49 01,498	764	734	107 0	54 5	52 4						
14	June 15, 1923	8	M	19 5	Encephalitis	+	35 01,635	1,062	572	83 8	54 5	29 3	506	574	380			
15	June 20, 1923	1	M	13 1	Pneumonia	+	31 21,160	800	360	88 6	61 0	27 7	491	552	356			
16	December 12, 1922	1	F	12 2	Pneumonia	+	31 0	905	281	74 0	51 0	23 0						

17	June	6 1923	4	M.	20 9	Pneumonia	+	35 0	1,870	1,215	655	89	458	131	3	523	598	386	
18	June	25, 1923	4	M.	15 6	Pneumonia	+	36 0	1,275	816	459	81	752	329	4	450	524	319	
19	June	5, 1923	6	M.	25 0	Pneumonia	+	57 13	1,600	1,355	1,805	126	054	272	5	448	494	414	
20	June	1 1923	7	M.	18 2	Pneumonia	+	30 3	1 542	1,077	464	84	759	225	4	427	487	287	
21	July	3, 1923	7	M.	16 4	Pneumonia	+	32 0	1,225	833	392	74	650	723	9	435	494	312	
22	July	7, 1923	7	M.	19 0	Pneumonia	+	35 0	1 324	860	464	69	645	224	4	435	509	268	
23	June	23, 1923	10	M.	22 2	Pneumonia	+	37 0	1,667	1 050	617	75	247	427	8	503	585	362	
24	December	28 1923	12	M.	30 0	Pneumonia	+	40 52	503	1,494	019	83	749	734	0	391	464	284	
25	June	6 1923	10	F.	27 5	Convalescent	0	37 0	1 980	1 248	732	72	045	426	6	438	485	360	
26	May	14 1925	9	M.	23 6	Pneumonia	+	38 51	523	937	585	64	539	724	8				8 680 5 3 4
27	December	29 1922	12	M.	31 8	Pneumonia	+	43 02	740	1 560	1 180	86	049	037	0	455	563	312	
28	January	28 1925	3	M.	12 05	Pneumonia	+	32 8	893	600	293	74	149	824	3	540	575	469	8 349 8 4 1

of pyelitis, three cases of typhoid fever and four miscellaneous febrile patients. The results are given in detail in the accompanying tables. In interpreting the results, the facts brought out in the first paper must be kept in mind. The plasma volume is more constant than the blood volume and is 50 ± 5 milliliters per kilogram of body weight except for children under three years of age when it is about 60 milliliters per kilogram. But the plasma volume in early life, in general, is less constant than in adults. The red cell volume tends to average about 30 milliliters per kilogram of body weight, though considerable variation is found.

The purest examples of a febrile state reported in this paper are the cases of typhoid fever, and the results are consistent in that they all show slightly high plasma volumes during the fever. Case 1 shows 62 and 58 milliliters of plasma per kilogram, case 3, 54 milliliters per kilogram and case 2, 59.5 milliliters during the fever and 40 milliliters during convalescence. It should be noticed that in case 2, there is an actual loss of total plasma from 922 to 654 milliliters and that the change in weight does not account for the change in the proportion of plasma. When it is taken into account that there is a retention of water in fever, the high plasma volumes per kilogram of body weight found in the other typhoid cases indicate definite increase in the total plasma.

The seven cases of pyelitis may be considered examples of less marked and prolonged fever. All show slightly high or normal plasma volume except cases 8 and 9. Case 8 had a low normal plasma volume of 45.7 milliliters per kilogram of body weight and case 9 the definitely low plasma volume of 35.5 milliliters. No other distinction of this case from the others was found except the slightly high concentration of the plasma chlorides.

The miscellaneous group consisting of one patient with thoracic empyema, one with influenza, one with tuberculous meningitis and one with encephalitis shows essentially normal plasma volumes.

The cases of primary pneumonia show rather confusing results especially if one considers only the results obtained on patients on whom a single determination was made during fever. The cases on which determinations were made after, as well as before the crisis, make an interpretation of the results from the former group of patients

possible and for this reason, the latter are tabulated separately. Fourteen isolated observations of the blood volume during lobar pneumonia were made. One would like to relate the plasma volume during fever to the weight just before the illness or at least to the weight after recovery. This might give a correction for the water retained diffusely throughout the body. The magnitude of this imperceptible retention of water was not appreciated at first and for this reason, the blood volumes are compared to the weight during fever. Studying the fourteen cases in this manner, ten show essentially normal plasma volumes, two high and two low plasma volumes. Case 16 shows 51 milliliters per kilogram as compared to a normal for her age of 60 milliliters, case 26, 40 milliliters as compared to the normal of 50 milliliters, cases 17 and 20 show 58 and 59 milliliters respectively as compared to the normal of 50 milliliters. However, when one considers that most of the patients with lobar pneumonia take on an appreciable amount of water, it will be seen that in most instances the plasma volumes must have been increased slightly.

The latter point is brought out fairly well in table 2 in which the results during fever and convalescence in the same patient are shown. Patient 29 showed 56 and 51 milliliters per kilogram in two determinations before the crisis and 49 milliliters per kilogram after the crisis. However, there actually was a decrease of about twenty per cent in the plasma volume since the febrile volumes were 894 and 816 milliliters and the afebrile volume 670 milliliters. The loss of weight from 16 to 13.6 kilograms masks the extent of the change when the plasma volume is related to the weight. Case 30 shows little actual change in the plasma volume but due to the loss of weight, the plasma volume increased from 67.5 and 72 milliliters during the fever to 79 milliliters per kilogram during convalescence. This case is unusual in that the plasma and cell volumes are so high under normal conditions. No explanation for this could be found. In case 31, the change in weight from 21.25 to 17.7 kilograms masks the loss of plasma volume from 884 to 820 milliliters, as the plasma volume per kilogram of body weight was 41.6 milliliters during fever and 46 milliliters during convalescence. Case 32 shows a decrease from 880 to 685 milliliters in plasma volume (68 to 56 milliliters per kilogram), and case 33, a decrease from 1,607 to 1,320 milliliters (69 to 59 milliliters per kilogram).

TABLE 2

Case	Date	Age yrs	Sex	Weight kg	Diagnosis	Fever	Blood volume— total			Blood volume per kilogram of weight			Chloride per 100 ml			Serum protein		
							Blood	Plasma	Cells	Blood	Plasma	Cells	Blood	Plasma	Cells	Per cent	Grams	Grams per kilogram
29	January 5, 1923	5	M	16 0	Pneumonia	+	1,400	894	507	87	655	831	7	431	508	296		
29	January 11, 1923	5	M	16 0	Pneumonia	+	1,300	816	484	81	351	030	2	418	518	250		
29	January 19, 1923	5	M	13 6	Convalescent	0	975	670	304	71	649	222	3	484	570	294		
30	November 21, 1923	10	M	30 0	Pneumonia	+	3,533	2,016	1,518	118	067	550	5					
30	November 23, 1923	10	M	30 0	Pneumonia	+	3,790	2,160	1,630	126	072	054	0					
30	December 5, 1923	10	M	28 4	Convalescent	+	3,750	2,250	1,500	132	079	352	8	460	595	258		
31	January 29, 1925	6	M	21 25	Pneumonia	+	1,352	884	468	63	641	622	0		490		8 61	76 13 58
31	February 5, 1925	6	M	17 7	Convalescent	0	1,330	820	510	75	146	328	7				7 67	62 93 55
32	February 21, 1927	3	M	12 95	Pneumonia	+	1,188	880	308	91	868	023	8		591		7 42	65 35 04
32	March 1, 1927	3	M	12 3	Convalescent	0	985	685	299	80	055	624	3				7 63	52 34 25
33	February 21, 1927	7	M	23 3	Pneumonia	+	2,125	1,607	522	91	469	022	3				6 55	105 04 5
33	February 25, 1927	7	M	22 25	Convalescent	0	1,869	1,320	548	83	859	324	6		586		7 85	103 54 65
34	February 14, 1927	3 5	M	14 9	Pneumonia	+	1,448	970	478	97	365	232	1		536		7 68	73 04 9
34	February 19, 1927	3 5	M	15 0	Convalescent	0	1,466	1,000	466	97	866	631	0		532		7 42	74 24 94
2	May 29, 1923	8	M	15 5	Typhoid	+	1,375	922	454	88	859	529	2					
2	June 15, 1923	8	M	16 2	Convalescent	0	1,027	654	373	63	440	423	0		308	449	240	
															466	516	377	

Essentially no change is found in case 35. Thus it is seen that there is usually a moderate increase in plasma volume in children with primary pneumonia, but in most cases the imperceptible retention of water is sufficient to mask the increase in plasma volume when the volume during fever is compared to the weight during fever. In four of the six cases studied before and after the crisis, there was an appreciable fall in the absolute plasma volume, after recovery, from the high level found during fever. A higher plasma volume during fever was found also in the only case of typhoid fever studied after recovery.

The chloride concentration of the plasma is a valuable guide to the extent of the physico-chemical changes which have taken place in the pneumonic patients studied. Most of the patients with fever and pneumonia had low plasma chloride concentrations. This would indicate that the physico-chemical changes described in adult lobar pneumonia (14) have taken place in these patients. No relation between the plasma chloride concentration and the plasma volume could be found. It should be noted that the plasma chloride concentration is quite low in the typhoid patient, case 2, and in cases 5, 6 and 8 of pyelitis. There probably is a tendency to low plasma chloride concentration in other fevers beside pneumonia, though sufficient data are not at hand to prove this point.

Chart 1 shows the relation of the plasma and cell chloride concentrations. Part 1 represents the results on the normal children reported in the first paper (15) and Part 2 the results on the febrile patients of this paper. It will be noticed that the cell chloride concentrations in the normal and febrile patients are distributed over the same range of values in both groups—200 to 450 milligrams per 100 milliliters. However, in the febrile groups, the low plasma chloride concentrations tend to be accompanied by low cell chloride concentrations so that there is a tendency of the group to fall along a straight line when represented as in chart 1. There are a number of exceptions so that many cases fall off the line. Evidently though other factors affect the relation of the cell and plasma chlorides, in febrile patients the concentrations of both the cell and plasma chlorides tend to be low.

A satisfactory explanation of the low plasma chloride values found in lobar pneumonia has never been given. Referring to table 2, it will be noticed that the increase in plasma volume is of such a magni-

tude that the additional water could account for the lowering of the concentration of chlorides if we assume no increase in the total chlorides of the body has taken place. Actually there is chloride retention during the febrile stage of pneumonia and release of chlorides after the crisis. Apparently the retention of water in the tissues is great enough to account for not only the retention of chlorides in the body as a whole, but also leads to depletion of the blood chlorides. The lowering of blood chlorides is probably augmented by the increase in plasma volume. In case 29, complete data are given and one can calculate the total chlorides of the blood and plasma. During the fever there were 6 and 5.4 grams of sodium chloride in the blood and

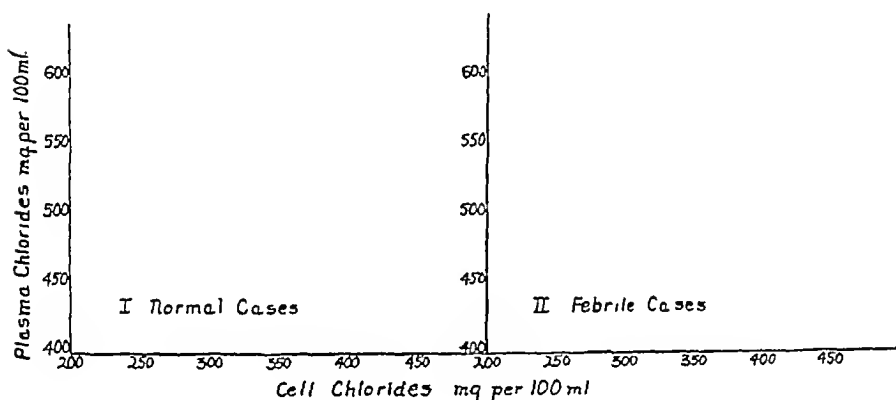


CHART 1 THE RELATION OF THE PLASMA CHLORIDES TO CELL CHLORIDES IN NORMAL CHILDREN AND IN CHILDREN WITH FEVER

4.5 and 4.2 grams of sodium chloride in the plasma, while during convalescence there were 4.8 grams of chloride in the blood and 4.2 grams of chloride in the plasma. Thus the blood dilution is great enough to account for a greater lowering of the chlorides than was actually found. Furthermore, the loss of weight after the crisis in cases 29, 30 and 31 is of such a magnitude that assuming the loss of weight to indicate water retained during fever, one can thereby account for not only the low concentration of plasma chlorides, but also the fact that an increased concentration of chlorides has not been found elsewhere in the body. Cases 32, 33 and 34 did not show the usual loss of weight after the crisis but they also did not show the

usual lowering of the plasma chloride concentration. However, cases 32 and 33 showed the usual drop in plasma volume after the crisis. These facts seem to indicate that the low concentration of plasma chlorides may depend chiefly on the retention of water during fever, and that the plasma volume change is not directly connected with the storage of water.

DISCUSSION

Three factors would seem to be at work in febrile states that might affect the plasma volume. (1) The higher metabolic rate would tend to increase the plasma volume, if the circulation rate remains constant. A higher metabolic rate would tend to make the venous carbon dioxide content show a greater elevation over that of the arterial blood than normal. As pointed out in the first paper of this series, the increased carbon dioxide content of the venous blood over that of the arterial blood, causes a greater increase in the osmotic pressure of the venous blood over that of the arterial blood than normal. This augments the tendency of venous blood to draw water from the tissues and should increase the plasma volume. (2) An increased rate of blood flow would tend to diminish the plasma volume. It is not certain whether there is an increased rate of blood flow in fever. However, in pneumonia and probably in other fevers also, the arterial and venous oxygen saturation becomes more nearly identical and as was pointed out earlier in this paper, this fact can be explained best by a rapid blood circulation. In the first paper of this series, the idea was developed that a rapid circulation would bring the arterial and venous carbon dioxide contents nearer to each other and thereby reduce the difference in osmotic pressure between arterial and venous serum. If the metabolic rate remains constant, this should reduce the amount of circulating fluid. (3) The carbon dioxide absorption curve would be at a lower level due to the higher temperature of the body (Stadie and Martin (16)) and hence the blood would be less efficient as a carbon dioxide and water carrier. From a study of the carbon dioxide absorption curves in other cases together with the blood volumes, minor variations in the carbon dioxide absorption curve seem to exert little or no influence on the plasma volume. However, with greater variations from the normal, changes take place in the plasma volume which may be explained by the changes in the dis-

sociation curve The level of the curve produces the changes in the plasma volume by altering the differences between venous and arterial carbon dioxide content If the level of the curve is lower, respirations tend to become more rapid so as to maintain the alkalinity of the blood by blowing off carbon dioxide Unless the circulation rate is changed, the difference between venous and arterial carbon dioxide content may remain the same With great lowering of the curve, however, the circulation evidently becomes more rapid, and the venous blood approaches the arterial blood in oxygen and carbon dioxide content as is attested by the reddish appearance of the skin Under these circumstances, the blood becomes concentrated This has been observed in diabetic acidosis where the hemoglobin concentration is often very great Fever alone produces only a slight variation in the carbon dioxide absorption curve and due to this fact, has practically no effect on the blood volume Nevertheless, certain children and babies react to fever with a severe acidosis due to other factors such as diarrhea, disturbed sugar metabolism leading to acetone body formation, etc , and some of these patients would probably show blood concentration

In ordinary fever such as studied in this series of cases, the first two factors seem to be the only ones affecting the plasma volume In a majority of the cases the increased metabolic rate has increased the plasma volume slightly, but this effect is probably diminished in most of the cases by a more rapid circulation and in some instances a rapid circulation may have even diminished the plasma volume

It should be remarked here that the changes found in this study are all relatively small and, though definite, are within the varying degrees of normality in all but a few instances The changes are not of such a nature as to suggest any therapeutic measures and are presented largely for their theoretic interest

SUMMARY

Blood volumes and blood chlorides are reported on febrile children three with typhoid fever, seven with pyelitis, twenty with primary pneumonia and one each with thoracic empyema, influenza, tuberculous meningitis and encephalitis In all forty-four, individual observations are reported

In fever, there is a slight to moderate increase in the plasma volume which is usually accompanied by a proportional increase in the water held diffusely throughout the body. Although the lungs are one of the chief organs of water excretion, the inflammation in primary pneumonia of children does not seem to bring about any changes in the water metabolism which are different from those seen in other fevers.

The data concerning the plasma chlorides in febrile conditions other than pneumonia, though incomplete, suggest that there is a tendency to a low concentration of the plasma chlorides in fever in general. In fever, a lowering of the concentration of the cell chlorides tends to occur when there is a lowering of the concentration of the plasma chlorides.

The retention of water in the plasma and throughout the body during pneumonia is great enough to explain the low chloride concentration of the plasma and the lack of an increased chloride concentration elsewhere in the body and the storage of chlorides during fever.

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BLOOD VOLUME IN NORMAL INFANTS AND CHILDREN

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Knowledge concerning blood volumes has been limited until recent years by the lack of any reliable method that could be applied to living patients. Information about the blood volume is desirable both for the study of anemia and of disturbances in the water metabolism. The work reported in this and the three subsequent papers was undertaken from the latter viewpoint.

There are two reliable methods of determining blood volumes which may be applied to patients. They are (a) the carbon monoxide method, first adapted to man by Haldane and Smith (1) and (b) the dye method of Keith, Rowntree and Geraghty (2). The former method gives results that are probably a little lower than the actual blood volume whereas the latter gives results a little higher than the actual blood volumes. The high results by the dye method have been shown by Smith (3) to be due to transfusion of part of the dye into the lymph. However, the amount of dye disappearing in the lymph is small and fairly constant and the method is accurate for comparative results.

Our knowledge of blood volumes has been recently reviewed by Erlanger (4). In the present paper, only such results as seem to concern this work will be mentioned. The findings of the various workers seem fairly concordant and indicate that adults tend to have about 50 milliliters of plasma and 83 milliliters of blood per kilogram of body weight, as determined by the dye method (Keith, Rowntree and Geraghty (2), Bock (5), Brown and Rowntree (6)). Bock has emphasized the fact that the plasma volume is more constant than the blood volume and has found it to be about 50 milliliters per kilogram of body weight in conditions showing such widely varying volumes of red cells as pernicious anemia and polycythemia. However, a minimum volume of red cells is necessary to maintain the plasma volume.

Robertson and Bock (7) found in soldiers who had lost large amounts of blood that the plasma volume returns quickly to normal unless the volume of the red cells has reached a certain low minimum. If the loss of the red cells is below this minimum, the plasma volume cannot be maintained until the red cell volume has been restored. Obese adults have low plasma volumes per kilogram of body weight (Brown and Keith (8)) but the plasma volume per square meter of surface area of obese adults was found to be essentially the same as for normal adults. A formula relating the blood volume to the surface area times a constant was worked out by Dreyer and Ray (9), the constant being different for different species of animals. These workers felt that since fat is a relatively avascular tissue, surface area would be a better measure of blood volume than weight.

Reports of actual blood volume determinations in infants are confined to three papers. None have been reported on older children. Lucas and Dearing (10) determined blood volumes by the dye method on infants during the first year of life. Their results expressed in milliliters per kilogram of body weight are: blood volume in newly born infants 107 to 195, average 147, plasma volume in newly born infants, 42 to 77, average 59, blood volume in older infants, 90 to 126, average 110, plasma volume, 57 to 78, average 67. In the first weeks of life, a wider variation in the plasma volume was found than later, and the whole blood volume was higher. However, the high whole blood volume in the newly born is entirely accounted for by the high volume of the red cells. The plasma volume is actually lower in the newly born than in infants over six weeks old. Bakwin and Rivkin (11) obtained similar results. They found the average for the blood volume to be 101 milliliters per kilogram of body weight and for the plasma 69 milliliters. In nineteen cases, the average blood volume was 1700 milliliters per square meter of surface area. Marriott and Perkins (12) found 91 cc of whole blood per kilogram of body weight in seven normal babies, under one year of age, and 80 cc per kilogram of body weight in babies with severe undernutrition. All the papers agree in finding slightly higher blood volumes per kilogram of body weight in babies than has been found in adults.

The blood volumes here reported were estimated by the method of Keith, Rowntree and Geraghty (2). The cell volumes were deter-

mined by hematocrit tubes made from small burettes which were 5 millimeters in diameter and calibrated. Oxalated venous blood kept under mineral oil was used to minimize the errors due to loss of carbon dioxide. Serum or plasma protein concentration was estimated in some of the later determinations by the Abbe refractometer (13). The surface area was computed by the formula of Lissauer (14) for the infants under one year of age. In the other patients, the surface area was obtained from the table of Benedict and Talbot (15) based on this formula.

The data of the present study were obtained from essentially normal infants and children. The older children were suffering from fractures, or had recovered from some minor illness. The babies had recovered from upper respiratory infections or were in the hospital for some minor complaint. Most of the infants were slightly undernourished and fed on modified cows' milk. The results reported here and to be reported in the subsequent papers indicate that moderate undernutrition makes no difference in the plasma volume per kilogram of body weight. The data found on these patients are given in detail in tables 1 and 2, but the general trend and significance may be appreciated best by examining the two charts.

Chart 1 represents the blood and plasma volumes in milliliters per kilogram of body weight as related to age. As there were not enough determinations to permit conclusions concerning the blood and plasma volumes during the first six weeks of life, the lower relative plasma volume at this age is represented in accordance with previous work (Lucas and Dearing (10) and Bakwin and Rivkin (11)). The plasma volume per kilogram of body weight as related to age describes a curve as indicated on chart 1. This curve starts at about 50 milliliters per kilogram of body weight and rises rather rapidly to 62 milliliters by the sixth month of life, remains high well into the second year, and then gradually returns to 50 milliliters by the beginning of the fourth year. Thereafter the plasma volume per kilogram of body weight agrees well with the adult figure, cited above. The whole blood volume tends to describe a similarly shaped curve, but, due to variations in the volumes of the red cells, the whole blood volume cannot be predicted very accurately. In general the blood volume per kilogram is 25 to 35 milliliters more than the plasma volume for the

TABLE 1

Case number	Date	Diagnosis	Sex	Age	Weight kgm	Sur face area sq m	Vol umes per cent of cells	Blood volume			Blood volume per kilogram			Blood volume per square meter of surface	
								Blood	Plas- ma	Cells	Blood	Plas- ma	Cells	Blood	Plas- ma
								ml	ml	ml	ml	ml	ml	ml	ml
1	July 26, 1923		F	1 wk	3 6	0 24	45 0	284	156	128	79 0	43 0	36 0	1,180	647
2	December 13, 1922		M	1 mo	3 4	0 23		221	221		65 0				950
3	July 13, 1923	Undernutrition	F	2 mos	3 1	0 21	27 0	214	156	58	69 0	50 4	18 7	984	710
4	July 20, 1923	Undernutrition	M	2 mos	4 2	0 27	27 5	301	218	83	71 7	52 0	19 7	1,120	814
5	September 10, 1923	Undernutrition	M	2 mos	3 5	0 24	27 0	271	198	73	77 7	56 5	21 1	1,180	835
6	April 7, 1924	Normal	M	6 wks	3 3	0 23		180			54 0				785
7	August 8, 1925	Normal	F	10 wks	3 7	0 24	30 0	321	225	96	87 5	61 1	26 0	1,340	920
8	December 3, 1922	Undernutrition	M	3 mos	3 0	0 21	19 0	240	194	46	80 0	64 5	15 3	1,140	905
9	December 1, 1922	Undernutrition	M	3 mos	4 2	0 27	34 0	400	264	136	95 3	63 0	32 4	1,480	985
10	November 29, 1922	Undernutrition	M	3 mos	3 0	0 21	25 0	215	161	54	71 6	53 6	18 0	1,020	753
11	September 17, 1923	Undernutrition	F	3 mos	3 5	0 24	24 0	246	188	58	70 3	53 7	16 5	1,040	794
12	July 12, 1923	Normal	F	5 mos	4 7	0 29	34 5	389	255	134	82 6	54 3	28 5	1,340	883
13	July 19, 1923	Normal	F	5 mos	4 3	0 27	29 0	372	264	108	86 5	61 4	25 2	1,380	967
14	September 13, 1923	Normal	F	6 mos	5 4	0 32	28 4	475	340	135	88 0	63 0	25 0	1,530	1,070
15	September 19, 1923	Undernutrition	F	9 mos	7 2	0 38	33 5	662	440	222	91 8	61 0	30 8	1,740	1,145
16	September 20, 1924	Undernutrition	F	1 yr	5 5	0 32	28 5	475	340	135	86 7	62 0	24 7	1,480	1,060
17	November 27, 1925	Normal	M	1 yr 2 mos	10 5	0 50	35 5	969	624	345	92 3	59 5	32 9	1,940	1,250
18	December 1, 1925	Normal	M	1 yr 2 mos	8 6	0 44	29 0	665	473	192	76 5	55 0	22 4	1,510	1,078
19	December 17, 1925	T B adenitis	M	1 yr 2 mos	9 5	0 47	32 6	739	498	241	77 8	52 5	25 4	1,570	1,060
20	December 10, 1925	Undernutrition	M	1 yr 2 mos	6 3	0 34	28 0	511	368	143	81 1	58 4	22 7	1,500	1 080
21	December 8, 1925	Undernutrition	M	1 yr 4 mos	9 6	0 46	30 0	647	453	194	67 4	47 2	20 2	1,410	986
22	September 15, 1923	Normal	M	1 yr 6 mos	10 0	0 49	31 1	897	618	280	89 8	61 8	28 0	1,830	1,260
23	June 23, 1923	Normal	M	2 yrs	12 6	0 57	34 2	1,058	696	362	84 0	55 3	28 7	1,860	1,220

24	September 14, 1923	Normal	F	2 yrs.	14 0	0 62	30 61, 038	720	318	74 0	51 4	22 71	670 1, 160
25	December 6, 1924	Undernutrition	F	2 yrs.	7 2	0 39	46 0	759	408	351 105 2	56 5	48 61	940 1, 050
26	December 10, 1924	Undernutrition	F	2 yrs.	8 6	0 44	30 0	672	470	202 78 4	54 8	23 61	530 1, 068
27	September 21, 1923	Normal	M	2 7 yrs.	13 0	0 59	37 51	024	640	384 78 8	49 2	29 61	740 1, 085
28	September 22, 1923	Normal	M	3 yrs.	14 6	0 63	30 2	960	670	290 65 7	46 0	19 81	540 1, 060
29	July 7, 1923	Normal	F	4 yrs.	15 0	0 65	38 01	200	744	456 80 0	49 6	30 41	840 1, 140
30	June 19, 1923	Normal	M.	5 yrs.	14 4	0 63	36 41,	170	745	426 81 4	51 7	29 61	850 1, 185
31	July 10, 1923	Normal	M	5 yrs	27 2	1 00	31 91,	982 1, 350	632	72 9	49 6	23 21	982 1, 350
32	June 5, 1923	Normal	F	6 yrs.	24 0	0 92	43 42,	340 1, 327	1, 013	97 5	55 3	42 32	540 1, 440
33	June 27, 1923	Normal	M	6 yrs.	20 0	0 83	34 71	347	880	567 67 4	44 0	23 41	630 1, 065
34	July 25, 1923	Normal	M	6 yrs.	18 4	0 76	34 01	394	926	474 75 7	50 0	25 71	840 1, 210
35	August 2, 1923	Normal	M.	6 yrs.	19 0	0 79	33 51,	407	936	471 74 0	49 2	24 81	780 1, 180
35	August 6, 1923	Normal	M	6 yrs.	18 4	0 77	33 51,	407	936	471 76 4	50 8	25 61	820 1, 210
36	July 21, 1923	Normal	M	6 yrs.	17 0	0 74	33 61	327	880	447 78 0	51 7	26 21	790 1, 190
37	June 8, 1923	Normal	F	7 yrs	21 0	0 84	34 41,	450	951	499 69 0	45 3	23 71	720 1, 134
38	June 13, 1923	Normal	F	7 yrs	18 9	0 76	31 41,	430	981	449 75 7	51 9	23 81	880 1, 290
39	July 12, 1923	Normal	M	7 yrs.	24 1	0 93	34 01,	818 1, 200	618	75 4	49 8	25 61	950 1, 290
40	July 10, 1923	Normal	M.	8 yrs.	22 2	0 88	36 01	595 1, 020	575	71 8	46 0	25 81	810 1, 160
41	July 11, 1923	Normal	M	8 yrs.	28 4	1 06	35 42	150 1, 390	760	75 8	49 0	26 82	020 1, 310
42	July 20, 1923	Normal	M	8 yrs.	27 2	1 05	33 62,	119 1, 404	713	77 9	51 6	26 22	020 1, 340
43	July 28, 1923	Normal	M	8 yrs	23 0	0 906	38 01,	761 1, 092	669	76 6	47 5	29 01	945 1, 200
44	August 1, 1923	Normal	M	8 yrs.	23 4	0 91	31 81	870 1, 275	595	80 0	54 5	25 42	030 1, 400
45	July 10, 1923	Normal	M	9 yrs.	22 7	0 89	37 01,	676 1, 056	620	73 8	46 5	27 31	880 1, 190
46	July 19, 1923	Normal	F	9 yrs.	21 5	0 82	37 01	562	984	578 72 6	45 8	26 81	900 1, 200
47	July 23, 1923	Normal	M	9 yrs.	24 0	0 93	37 01	911 1, 204	707	79 8	50 3	29 52	030 1, 290
48	July 4, 1923	Normal	M	10 yrs.	24 5	0 94	35 01,	877 1, 220	657	76 6	49 7	26 82	060 1, 300
49	July 5, 1923	Normal	F	10 yrs.	29 0	1 05	38 02	338 1, 450	888	80 6	50 0	30 62	220 1, 380
50	July 23, 1923	Normal	M.	10 yrs.	33 0	1 18	39 02	598 1, 584	1, 014	78 7	48 0	30 72	200 1, 340
51	July 28, 1923	Normal	M	10 yrs.	22 3	0 84	38 01,	826 1, 132	694	81 9	50 8	30 12	180 1, 350
52	July 25, 1923	Normal	M	11 yrs.	30 0	1 11	33 02,	240 1, 500	740	74 7	50 0	24 62	090 1, 350

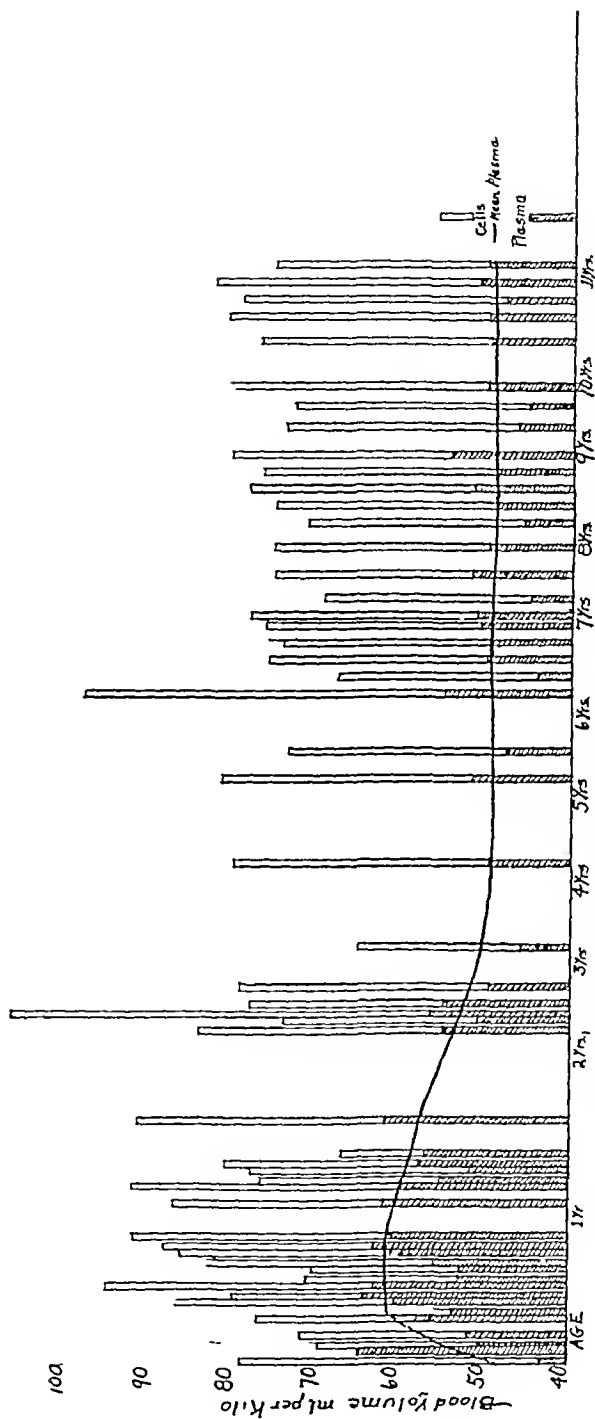


CHART 1 THE RELATION OF BLOOD AND PLASMA VOLUMES PER KILOGRAM AT DIFFERENT AGES

respective age. An exception to this statement is not shown in chart 1, but is brought out best in the paper of Lucas and Dearing (10). During the first 3 to 4 weeks of life, the proportion of the blood represented by the red cells is 45 to 70 per cent, while during the rest of the first year of life, it is only 30 per cent. The high proportion of red cells makes the total blood volume correspondingly high. It will be noticed also that the plasma volume per kilogram of body weight varies more widely during the first year of life, than later. This variability cannot be explained from our present knowledge of infant physiology. This physiological constant must, therefore, be classified with the other physiological constants that manifest greater variability in infants than in adults.

TABLE 2

Case number	Protein		Case number	Protein	
	Per cent	Grams per kilogram		Per cent	Grams per kilogram
5	6.62	3.74	19	8.65	4.54
7	7.96	4.86	20	6.98	4.08
16	7.26	4.50	21	8.05	3.80
17	7.42	4.40	25	7.78	4.40
18	7.63	4.20	26	9.60	5.25

The red cell volume per kilogram of body weight after the first six weeks of life, is about 25 to 35 milliliters. This is somewhat lower than in adults, and is in keeping with the lower hemoglobin and red cell count.

The total serum protein per kilogram of body weight is given on a few cases in table 2. The average for the second year is 4.2 grams per kilogram of body weight, whereas Bakwin and Rivkin (11) found 3.6 grams for the first year. From our knowledge that the serum protein concentration remains about the same after the first year of life, one may assume that the average for the rest of life will be about 4 grams per kilogram of body weight. This figure, though probably not very exact, will be useful for comparison with the findings obtained from patients suffering from various diseases.

The blood and plasma volume per square meter of body surface as related to age is shown in chart 2. It is realized that the methods for

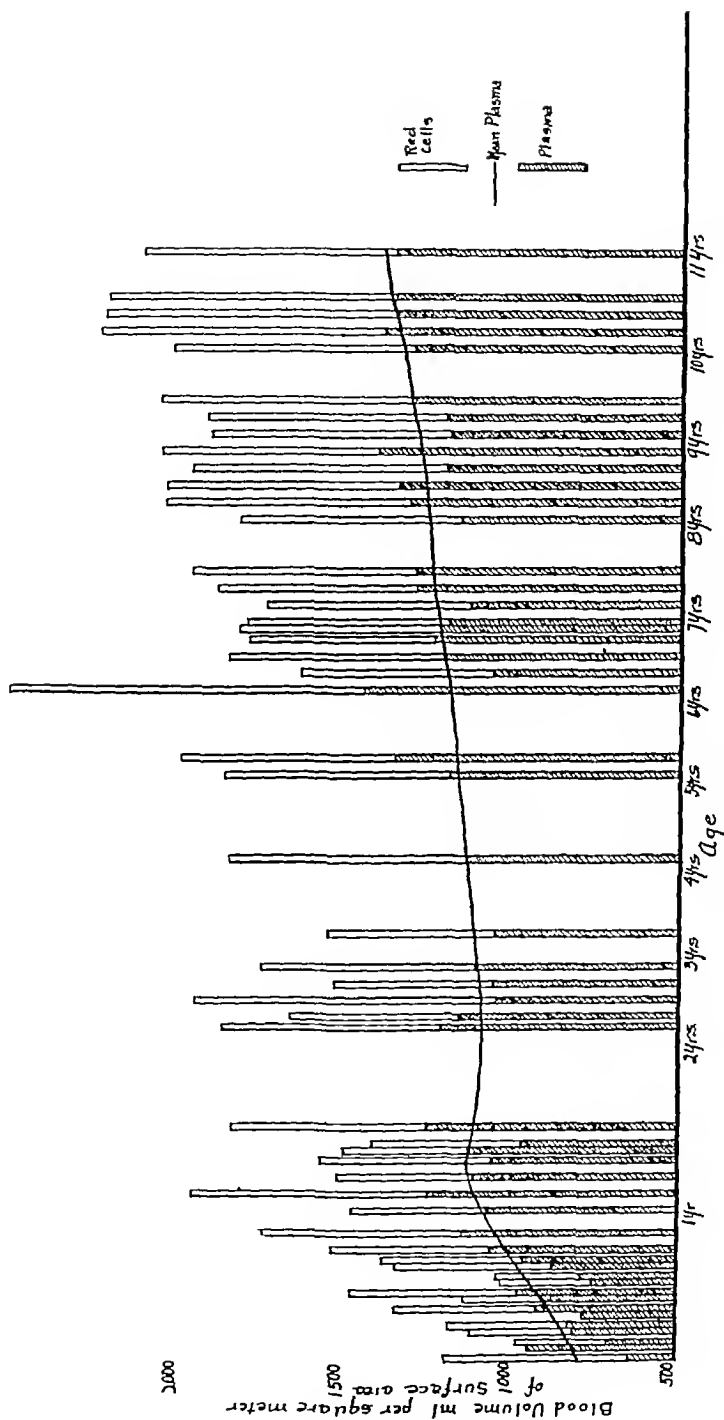


CHART 2 THE RELATION OF BLOOD AND PLASMA VOLUMES PER SQUARE METER OF SURFACE AREA AT DIFFERENT AGES

computing the surface area are not yet sufficiently accurate to give a very exact estimate of the surface area in a given child. However, the figures are sufficiently accurate to show the general relation of the blood and plasma volume to the surface area. As will be noticed, the plasma volume per square meter of body surface as related to age rises rapidly during the first year from 750 milliliters to 1110 milliliters and then remains constant during the second year, perhaps decreasing a little. Thereafter, there is a steady rise to about 1375 milliliters, by the twelfth year of life. That this rise continues till adult life is indicated by the fact that the adult average of the plasma volume per square meter of surface area is 2000 milliliters (Brown and Keith (8)).

The variability of the red cell volume makes the curve of the blood volume per square meter of surface area more irregular. In general the whole blood volume describes a curve similar in shape to the one described by the plasma volume.

The question as to whether weight or surface area is better correlated with the plasma volume has not been settled and the data in this paper only bring out new facts. Table 3 shows the standard deviation¹ from the average and the percentage standard deviation from the average of the plasma volume as related to both weight and surface area. The plasma volume per kilogram of body weight was not used in the six youngest babies in making this table because the data for this age are not sufficiently numerous. No figures are given for the first year for the standard deviation of the plasma volume per square meter of surface area because at this age the average plasma volume per square meter is changing too rapidly to allow such a computation from the data of this paper.

¹Standard deviation is calculated according to the well known formulae

$$\delta = \sqrt{\frac{\sum (x - x_1)^2}{n}}$$

δ = standard deviation

x = mean measurement

x_1 = given measurement

N = number of measurements

Σ = Sum of the different quantities $(x - x)^2$

Percentage standard deviation = $\frac{100\delta}{x}$

The average of the percentage standard deviations for each age is the same (5.4) whether plasma volume is compared with weight or surface area. However, since weight is more variable than surface area, the same degree of correlation would indicate a closer relationship between weight and plasma volume, than surface area and plasma volume. However, there are not enough cases in this series to draw conclusions from small differences. The main fact brought out is that surface area cannot be correlated with the plasma volume unless the age of the individual is also taken into account, but weight may be correlated with the plasma volume after the third year, since the plasma volume is constant at 50 milliliters per kilogram of body weight, after this age (see charts 1 and 2).

TABLE 3

	Age										
	1	2	3	4	5	6	7	8	9	10	11
Standard deviation per kilogram of weight	4.8	3.7	3.1	3.1	0	2.1	3.7	2.7	3.9	4.0	1.0
Percentage standard deviation per kilogram of weight	7.7	7.5	5.7	6.2	0	4.1	7.4	5.4	7.8	8.0	2.0
Standard deviation per square meter of surface		8.9	6.5	1.3	0	12.7	12.6	6.1	7.2	9.0	2.1
Percentage standard deviation per square meter of surface		7.3	5.9	1.3	0	10.9	10.5	4.9	5.7	7.0	1.5

DISCUSSION

The shape of the curve of the plasma volume per kilogram of body weight as related to age suggests a relationship between the plasma volume and the metabolic rate. It will be noted that the shape of this curve is similar to that of the basal metabolic rate per square meter of surface area as related to age (Benedict and Talbot (16)). There is both a rise in the metabolic rate and in the plasma volume during the first year of life and both remain high during the second year. The basal metabolic rate drops rather rapidly till the beginning of the fourth year and continues to decrease slowly during the rest of childhood. The plasma volume per kilogram of body weight decreases rapidly till the fourth year but then seems to be quite constant.

However, the figures for adults tend to be slightly lower than those for children reported in this paper (see previous references) and the comparatively small number of cases reported here may not have been sufficient to indicate a slight tendency to a decrease in the plasma volume after the third year Thompson (17) found in nine patients with myxedema that treatment with thyroid extract caused an increase in the total plasma volume as follows average increase in the total plasma volume 22 per cent, average increase in the plasma volume per kilogram of body weight 28 per cent, average increase in plasma volume per square meter of body surface 22 per cent Furthermore, the plasma volume while the patients were suffering from myxedema, in general, was low These facts seem to indicate that the higher the metabolic rate, the larger the amount of water in the blood stream, and the lower the metabolic rate, the smaller the amount of water in the blood stream

The fact that the metabolic rate is so closely related to the surface area and that the surface area has a relation to the plasma volume which varies with the age of the child demands some explanation The work of Brown and Keith (8) on obese patients would lead one to expect a close correlation between plasma volume and surface area These facts may be reconciled by assuming that the plasma volume is related primarily to the mass of the body tissues and that there is only a secondary relation between the plasma volume and the metabolic rate Thus weight becomes the better measure of the plasma volume when individuals of widely different sizes are chosen, but with individuals of about the same weight, the surface area may be a better measure of the plasma volume than weight

The red cells play an important part in the regulation of the blood volume In normal individuals, the volume of the red cells is large enough to maintain the plasma volume However, a minimum volume of red cells is necessary to carry and hold water in the blood stream (Robertson and Bock (7) Keith (18)) The dependence of the body on red cells to transport water is suggested by the appearance of edema in severe cases of anemia Based on the increased depression of the freezing point which accompanies an increase in the tension of the carbon dioxide to which blood is exposed, Buckman and Darrow (19) have advanced the hypothesis that amongst the other varied

functions of the red cells must be added that of being the chief carrier of water

The mechanism of maintaining and carrying the blood and plasma water may be explained in part as follows. Given an adequate volume of red cells circulating through the body, the following events tend to take place. When the oxygenated blood reaches the systematic capillaries, a certain amount of fluid is filtered out of the blood stream by hydrostatic pressure, the red cells lose oxygen and take up carbon dioxide, as a result of the increased tension of carbon dioxide. This causes an increase in the osmotic pressure of the plasma and presumably of the red cells which become swollen with water taken from the plasma. The increased osmotic pressure of the plasma enables it to take up water from the tissues to replace the loss of water to the red cells. In the lung capillaries all the factors favor an accumulation of water in the pulmonary tissues. In addition to the hydrostatic filtration process, the loss of carbon dioxide decreases the osmotic pressure of the plasma and thus favors the transfusion of water into the alveolar tissues. This probably accounts for the fact that the lungs contain a higher proportion of water than any other body tissue. The extent of the tendency of the circulating blood to take up water from the systemic tissues will depend ultimately on the amount of carbon dioxide carried by the blood. Although, in the plasma alone, bicarbonate is formed on exposure to carbon dioxide, and this reaction is accompanied by an increase in the osmotic pressure and is a reversible reaction, it is the presence of hemoglobin in the red cells, which so greatly enhances the efficiency of this reaction. The hemoglobin under the influence of carbon dioxide loses oxygen and becomes more alkaline, and conversely, the presence of oxygen frees carbon dioxide through the formation of oxyhemoglobin which is more acid than reduced hemoglobin. This property of hemoglobin explains the efficiency of blood not only as a carbon dioxide but also as a water carrier. Thus the amount of water taken up by the blood from the tissues should be related to (1) the amount of carbon dioxide produced or the basal metabolic rate and (2) the efficiency of the blood as a carbon dioxide and water carrier which under ordinary circumstances is dependent on the circulating mass of red cells.

Based on the above described mechanism of water transport, one

may conceive of six classes of disturbances which may affect the blood volume and water distribution. They are as follows: (1) disturbances in carbon dioxide production as in diseases of the thyroid gland, fever, etc., (2) disturbances of the transporting mechanism of the blood such as occurs in anemia and changes in the acid base equilibrium leading to too high or too low initial bicarbonate levels, (3) disturbances in carbon dioxide and water excretion in the lungs, as in emphysema, pulmonary edema, heart disease, pneumonia, etc., (4) disturbances in the excretion of water by the sweat glands, gastrointestinal canal and kidneys as in heat stroke, diarrhea and perhaps some forms of nephritis, (5) disturbances in the water absorption as in vomiting, and perhaps some forms of diarrhea, (6) disturbances in the rate of blood flow.

The manner in which all the above types of disturbances may affect water balance is fairly obvious, and only the third and sixth need any elaboration. Since venous blood undergoes an increase in osmotic pressure over that of arterial blood which is directly proportional to the increase in bicarbonate content, it is apparent that the tendency of the venous blood to take up water from the tissues depends on the increase in the bicarbonate content of the venous blood over that of the arterial blood, what one might call the potential difference between arterial and venous blood. In some unpublished experiments by Buckman and Darrow it was found that an increase in bicarbonate of the plasma of one volume per cent is accompanied by a lowering of the freezing point of about 0.001 degree centigrade. This corresponds to an increase in osmotic pressure of 9.1 millimeters of mercury, and when one takes into account the usual difference in bicarbonate content of venous and arterial blood, one would expect an increase in osmotic pressure of venous blood over that of arterial blood of the same order of magnitude as the fall in hydrostatic pressure from arterial to capillary blood. It is obvious that, with the same rate of carbon dioxide production, the difference in bicarbonate content between arterial and venous blood will become less the more rapid the rate of blood flow. If the increase in bicarbonate or osmotic pressure becomes small enough, an equilibrium between the osmotic pressure of the tissue and plasma cannot take place in the short period of time that it takes the blood to pass through the tissues. Since hydrostatic

pressures remain about the same, water tends to accumulate in the tissues at the expense of the plasma under such conditions. Apparently this is what happens with a too rapid rate of blood flow. Similarly with a slow circulation, the increase in osmotic pressure may be great enough to increase the rate of water diffusion back into the plasma. Thus, when the water carrying mechanism of the blood is compensated, apparently a slow rate of blood flow leads to increased plasma water content, and diminished tissue water content, whereas a rapid rate of blood flow leads to a diminished plasma water content and an increased tissue water content. However, due to the shape of the carbon dioxide curve, which shows diminishing increments in bicarbonate with increasing carbon dioxide pressure, the carbon dioxide carrying and water carrying mechanism would tend to break down with too slow a rate of blood flow, and, in such cases, one would expect an accumulation of water in both the tissues and plasma. Data supporting these views will be given in subsequent papers in cases of pneumonia and heart disease.

When carbon dioxide excretion is interfered with in the lungs, as in cases of pulmonary edema, the first obvious change in the blood is an increase in arterial bicarbonate and decrease in arterial oxygen. This lessens the difference in bicarbonate content of venous and arterial blood by making the blood work at a higher carbon dioxide pressure, and as noted above, this diminishes the efficiency of the carbon dioxide and water carrying mechanism of the blood. Thus pulmonary edema leads to diminished plasma water content, and increased tissue water content. Evidence of these changes is given in post-influenzal pneumonia and poisoning by war gases by Underhill and Ringer (20) and Underhill (21). In emphysema, the increased red cell concentration leads to greater efficiency of the carbon dioxide and water carrying mechanism of the blood. Only experimental observations can tell whether this is sufficient to overcome the tendency to diminished plasma volume one would otherwise expect.

The above mechanism can only be considered a partial explanation of the transportation and distribution of water. Increased pressure of carbon dioxide in the tissues increases the osmotic pressure of the tissues by a process similar to that observed in the blood, and thus alters the water distribution. Other means of varying the salt binding

power of proteins must occur, but little is known of such processes. Furthermore, our present knowledge does not permit a discussion of the rôle played by differential excretion of electrolytes and other crystalloids by the kidneys, intestines and sweat glands. Also any disturbance in the distribution of colloids should produce a disturbance in the water balance. No explanation of water metabolism can be complete, without considering these factors in addition to the mechanism postulated in this paper.

SUMMARY

Blood volumes determined by the dye method are reported on normal infants and children up to twelve years of age. A curve of the plasma volume per kilogram of body weight as related to age shows a rise in the plasma volume from 50 to 62 milliliters during the first year of life, and a return to 50 milliliters, by the fourth year. Thereafter, the plasma volume remains constant at 50 milliliters per kilogram of body weight.

A curve of the plasma volume per square meter of surface area as related to age shows a rapid rise from 750 to 1100 milliliters during the first year of life, and thereafter there is a gradual increase to 1375 milliliters by the twelfth year.

The proportion of the blood represented by the red cells is about 30 per cent, except during the first six weeks of life, when it is 45 to 70 per cent. The whole blood volume cannot be predicted very accurately either from the weight or the surface area because of the variability of the cell volume.

The following hypotheses are advanced: (1) The amount of plasma is primarily dependent on the mass of the body tissues. (2) Within certain limits set by the mass of the tissues, the amount of water in the blood stream varies directly with the metabolic rate.

The mechanism by which the plasma volume is maintained and varied is given a partial explanation.

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A COMPARATIVE STUDY OF THE EFFECTS OF VARIOUS TREATMENTS ON THE CALCIUM AND PHOSPHORUS METABOLISM IN TETANY

I CHRONIC JUVENILE TETANY

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The problem of tetany has been of considerable interest to both clinicians and experimental workers. The variety of clinical conditions with which tetany is associated, and the divergent chemical findings in the blood which various types of tetany manifest, indicate that this condition is merely a clinical syndrome varying widely in etiology as well as in mechanism of production in the different types, although the final symptomatology may be identical. The importance of calcium in the pathogenesis of tetany has long been recognized (1). In infantile tetany (2), commonly occurring in children with rickets, there is a disturbance in the calcium metabolism with lowering of blood calcium. When a cure of tetany results, as from cod liver oil or ultraviolet radiation, the blood calcium rises. Similar disturbance in calcium metabolism takes place in tetany parathyreopriva (3), either experimental or following accidental removal of the parathyroid glands during thyroid operations. In gastric (4), bicarbonate (5), or hyperpneic tetany (6), however, the blood calcium remains normal, while the bicarbonate of the blood is increased with a tendency toward an alkaline reaction. Freudenberg and György (7) in attempting to harmonize these discordant observations, state that the essential element in tetany is the concentration of ionized calcium in the blood. Rona and Takahashi (8) showed that the calcium ion concentration in the blood depends not only on the actual concentration of the total calcium, but also on the bicarbonate and hydrogen ion concentrations according to the following equation

$$\frac{(Ca^{++})(HCO_3^{-})}{(H^{+})} = K$$

Theoretically, an increase of bicarbonate ion concentration toward an alkaline reaction as occur in gastric, but hyperpneic tetany, tend to diminish the calcium ions in thereby cause the symptoms of tetany

As there is at present no available method of directly calcium ion concentration in the blood, many attempts made to separate serum calcium into diffusible and non-diffusible portions, thus indirectly, perhaps incompletely, gain the state of calcium in the blood. Different methods for the purpose have yielded different results as discussed in the literature on the subject (9). The overwhelming evidence seems to support the view that it is the diffusible rather than the non-diffusible calcium that is physiologically important in the control of neuromuscular irritability and that it is the diffusible fraction that is deficient in tetany, although Cruickshank (10), and Cameron and MacCallum (11) conclude that in tetany parathyreopriva the reduction is mainly in the non-diffusible fraction. Von Meysenbug (12), and Moritz (13) found that both the diffusible and non-diffusible calcium were reduced in the same ratio.

Recent experiments in the treatment of tetany have been largely in the effort to throw light on the mechanism of the disease, but the effects of various treatments have not been systematically and quantitatively compared. MacCallum and Voegtlin (11) obtained immediate relief of symptoms from parathyroid tetany by intravenous injections of soluble calcium salt. These experiments emphasized the prime importance of sufficient calcium in the blood to maintain a normal neuro-muscular irritability. Acid-producing substances, which are supposed to increase the concentration of calcium, have also been tried in the treatment of tetany. Ross (14) administered hydrochloric acid, calcium ammonium chloride to children and showed that on the one hand the carbon-dioxide capacity of the blood is decreased and the hydrogen ion concentration increased without necessarily affecting the total serum calcium level. The therapeutic effects of the

Huldschinsky (15), Casparis and Kramer (16), and Hoag and his collaborators (17) have shown that ultraviolet radiation has remarkable effect in the treatment of infantile tetany and in raising the serum calcium, due probably to an increased absorption of calcium through the intestinal tract. Brown, MacLachlan and Simpson (18) treated seven cases of infantile tetany with equally good results. Liu (19), in studying the influence of cod liver oil on the calcium and phosphorus metabolism in tetany, found that cod liver oil, similar to ultraviolet radiation, increases the calcium retention and raises the blood calcium, thereby curing tetany.

With the advent of Collip's discovery (20) of a parathyroid extract active in raising the blood calcium of both normal and parathyroidectomized dogs, this treatment has been applied to human subjects. According to Greenwald and Gross (21) the injection of this extract increases the excretion of calcium both in the urine and feces in dogs. The co-existence of hypercalcemia and increased calcium output is taken to indicate that the parathyroid hormone mobilizes calcium from the tissues, chiefly the bones. In normal calves (22), the administration of parathyroid extract is followed by increased calcium and phosphorus excretion in the urine, but no consistent change in the feces. In the experiments of Stewart and Percival (23), it is demonstrated in cats that the main excretory route of calcium is the large intestine and that following the parathyroid extract injections, while the serum calcium remains elevated, there is no change in the excretion of calcium. Apparently there is considerable difference in opinion as to the mode of action of the parathyroid extract, partly on account of the different species of animals employed. The mode of action of this extract in man has not been definitely established, although its beneficial effects on parathyroid tetany (24) and infantile tetany (25) have been reported, and Hoag et al. (26) have obtained diminished calcium retention in one normal and three rachitic infants, and increased calcium retention in two cases of infantile tetany during the period of parathyroid extract administration.

The present communication has for its purpose the study and comparison of the effects of the various treatments on the calcium and phosphorus metabolism in two cases of chronic juvenile tetany, embodying the measurements of the intake and output of these ele-

ments in conjunction with their blood levels and the partition of serum calcium into diffusible and non-diffusible portions

EXPERIMENTAL SUBJECTS

The two subjects studied were girls, one aged 16, the other 17, each showing on admission to the hospital marked carpopedal spasm, Chvostek's sign, Trousseau's sign, and increased electrical reaction typical of tetany. They gave a history of repeated attacks of the same nature every winter for the past three or four years, with complete remissions in the summer. They came from an orphanage near Peking, containing about 400 boys and 330 girls varying from 5 to 22 years of age. Investigation in January, 1927, revealed that 34 per cent of the girls and 22 per cent of the boys were affected with tetany of varying intensity from active symptoms and signs to only a positive facial phenomenon without complaints. This exceedingly high incidence of tetany in the orphanage suggests the operation of some factor or factors that are related to the diet or conditions of living of its inmates. Hammond and Hsia (27) have carefully studied their living conditions as well as their diet. They state that they are living a happy useful life, working hard and playing actively. Their diet, consisting chiefly of millet, wheat and corn meals, is monotonous, there being no change except occasional substitution of vegetables in season. According to their estimates, children of 16 take daily about 18 grams of fat, 57 grams of protein and 380 grams of carbohydrate, with a total intake of approximately 1900 calories. Thus the protein intake is moderately low, the fat intake very low, and the carbohydrate intake correspondingly high. By calculating from the diet lists, the daily average calcium intake is approximately 0.15 gram and phosphorus intake 0.5 gram. Shohl and Sato (28) suggest that the average calcium requirement is 0.0153 gram per kilo of body weight per day, or 0.6120 gram for a person of 40 kilos (one subject weighing 41, the other 36 kilos). Ehrstrom (29) considers that the minimum of phosphorus required is 0.0261 gram per kilo per day, or 1.044 gram by a person of 40 kilos. According to these criteria, the intake of both calcium and phosphorus in the orphanage diet is very low. However, as shown presently, as well as from the seasonal incidence of tetany, calcium lack cannot be the sole cause of tetany in these cases.

METHOD OF INVESTIGATION

The two subjects were placed in the metabolism ward where carefully weighed diets with constant calcium intake, and complete collection of both urine and stools were ensured. Urine was collected as 24-hour specimens, and stools were marked off with carmine to correspond to 4-day periods. 0.5 gram of the dye being given by mouth at the same time of the day every four days. Calcium and phosphorus in urine were determined daily, and those in stools every four days. Throughout the experimental period they were on a diet with a constant daily intake of calcium, which was only slightly higher than the estimated value from their previous diets in the orphanage. The calcium and phosphorus values of some of the foods were taken from Sherman (30), and others obtained from analyses made in the laboratory of Dr. Hsien Wu of the Peking Union Medical College. Four varieties of treatments were given, namely, (a) hydrochloric acid, 10 per cent, from 4 cc. to 12 cc. daily, (b) calcium chloride, 20 per cent solution, 5 cc. twice a day, corresponding to 2 grams of calcium chloride, or 0.722 gram of calcium daily, (c) pure cod liver oil in 30 cc. daily doses, and (d) parathyroid extract (Collip) subcutaneously, 25 to 100 units daily, usually given in two injections. Each kind of treatment was given for two or three periods of four days each with one or two control periods before and after the treatment. Blood was always withdrawn before the noon meal from one of the arm veins, and estimated for calcium, phosphorus, chloride and carbon-dioxide capacity as well as for partition of serum calcium into diffusible and non-diffusible fractions.

Blood calcium was determined by the method of Tisdall as modified by Clark and Collip (31), phosphorus by that of Benedict (32). The method of Myers and Short (33) was employed for blood chloride and that of Van Slyke and Cullen (34) for carbon-dioxide capacity. The partition of serum calcium was studied with the method of Montz (13), modified by Updegraff, Greenberg and Clark (35), and the diffused and non-diffused calcium were separately determined. Briggs' method (36) was used for urinary phosphorus and Sbohl and Pedley's method for urinary calcium. The stools of each 4-day period were mixed, dried in an oven at about 110°C. to a constant weight, and ground into a fine powder. Exactly 2 grams of the dried stool were weighed in a platinum crucible and ashed to a whitish powder. The ash was dissolved in 0.1 N hydrochloric acid, and an aliquot portion taken for analysis of calcium and phosphorus. The calcium was determined by Clark and Collip's method (31) with the addition of 1 cc. of 20 per cent sodium acetate in the initial precipitation, and phosphorus by Briggs' method (36).

REPORT OF CASES

Case I Hospital No 15846 T. C. C., a Chinese girl of 16, was admitted to the Peking Union Medical College Hospital on January 19, 1927, for repeated attacks of numbness and spasm of hands and feet lasting about a month. For three years previously, she had had similar spasticity of hands and feet during the

however, did not last, and the signs of tetany recurred three or four days after the discontinuation of the treatment

For two periods calcium chloride was then given in 2 grams daily doses corresponding to a four-fold increase of the intake of calcium. The striking result was a large retention of calcium, amounting to 2.11 grams or 57.8 per cent during the first period and 1.67 gram or 46.1 per cent during the second. But the blood calcium was essen-

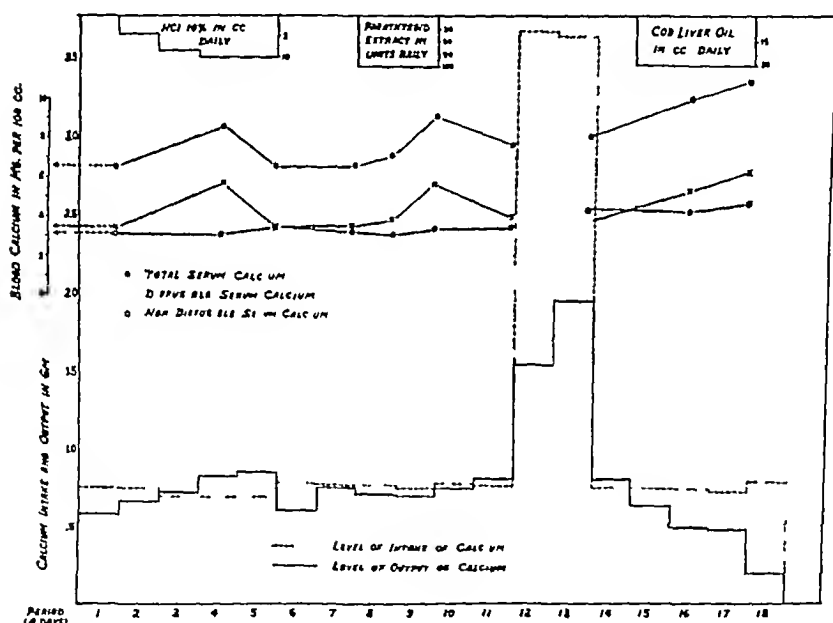


CHART 1 CASE I THE EFFECT OF VARIOUS TREATMENTS ON THE CALCIUM BALANCE, AND THE TOTAL, DIFFUSIBLE AND NON-DIFFUSIBLE SERUM CALCIUM

tially unchanged. There was no improvement whatsoever in the signs and symptoms.

The last treatment, namely, cod liver oil, seemed to be the most satisfactory. Three consecutive periods were devoted to this treatment. The relief of tetany was as complete and prompt as during the parathyroid extract period, but more permanent. Blood calcium was raised from 8.0 to 10.7 mgm, the increase occurring chiefly in the

diffusible portion Calcium was retained in increasingly greater amounts, and the retention of calcium seemed to be due to a reduction in its fecal excretion, as its elimination in the urine was slightly increased during the cod liver oil periods The effect of cod liver oil remained long after the treatment was stopped She was discharged well on April 18, 1927

Case II Hospital No 12947 L H T, a Chinese girl, aged 17, was admitted to the Peking Union Medical College Hospital on January 11, 1927, complaining of tonic spasm of fingers, hands, toes and feet for about two weeks Two years before, during winter months, she noticed numbness and stiffness of fingers, and with the onset of warmer months, she became symptom free A year ago, she entered the hospital for the same trouble with typical signs of tetany Her condition improved after ultraviolet radiation, serum calcium being raised from 8.5 to 9.7 mgm. She remained well until shortly before the present admission when a recurrence of tetany took place with spastic attacks of hands and feet more severe than before

She was well nourished but slightly undersized Weight 41 kgm., height 142 cm. Physical examination was essentially negative except for the presence of the classical signs of tetany She was not in an acute attack, but both Chvostek's sign and Trousseau's sign were positive and the electrical reaction showed hyper irritability Serum calcium was 8.8 mgm. per 100 cc. with 3.3 mgm. diffusible and 5.5 mgm. non-diffusible, phosphorus 3.12 mgm., sodium chloride 584 mgm., and carbon-dioxide capacity 67.2 per cent.

The patient was put on a diet similar to that of case I, and her first treatment was a series of parathyroid extract injections, 60 units daily for two periods Her blood calcium rose from 8.8 to 9.7 mgm., the rise being entirely in the diffusible fraction (table 2, chart 2) The retention of calcium increased slightly during the parathyroid extract periods With the elevation of blood calcium to almost normal level, especially the diffusible calcium, as well as the increase in calcium retention, her symptoms were entirely relieved, with disappearance of both Chvostek's and Trousseau's signs

After a rest period of four days, during which her symptoms returned, she was given hydrochloric acid for two periods With the acid administration, she experienced no relief whatsoever Her serum calcium dropped from 8.4 to 7.7 mgm. The calcium balance, positive previously and during the first acid period, became negative during the second acid period with an increased excretion of calcium both in the urine and feces

TABLE 2
Case II

Date	Treatment	Intake						Output						Balance		Retention		Blood serum				Plasma																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
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Calcium chloride, 2 grams daily, was given alone for two periods, and then combined with cod liver oil 30 cc. daily for another two periods. During the first two periods when calcium chloride alone was given, the treatment made no apparent difference to her symptoms and her blood calcium remained stationary, although there was a large retention of calcium. But during the second two periods when cod liver oil was added to calcium chloride, her blood calcium rose from 7.7 to 9.1 mgm with 5.0 mgm of diffusible calcium, coinciding with

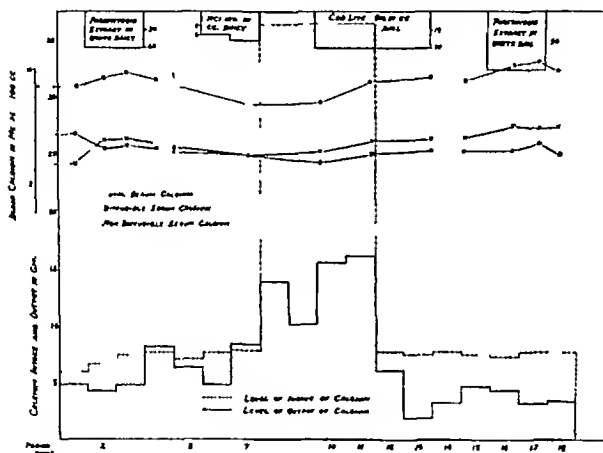


CHART 2 CASE II. THE EFFECT OF VARIOUS TREATMENTS ON THE CALCIUM BALANCE, AND THE TOTAL, DIFFUSIBLE AND NON DIFFUSIBLE SERUM CALCIUM

the disappearance of tetany. There was, however, no further increase in the retention of calcium with the aid of cod liver oil.

During the next two periods when cod liver oil alone was continued, her blood calcium continued to rise slightly. The striking change was the tremendous increase in the retention of calcium, amounting to 75 per cent of the calcium in the diet. This effect continued during the succeeding periods when cod liver oil was stopped.

Toward the end of the experimental period, when she was remaining free from symptoms, another course of parathyroid extract injections was given, 100 units daily for two periods. There was a slight increase in the blood calcium, namely, to 10.4 mgm with 58 mgm of diffusible calcium. The calcium output was decreased slightly resulting in a better retention than the control periods. The patient was discharged well on April 18, 1927.

DISCUSSION

It has been shown (9) that in normal individuals the total serum calcium of about 10 mgm per 100 cc is divided equally between the diffusible and the non-diffusible fractions. In case I with a total calcium of 6.6 mgm, there was a proportionate decrease in both fractions, while in case II, in whom the total calcium was slightly low (8.8 mgm), the reduction was mainly in the diffusible portion (3.3 mgm), the non-diffusible portion remaining normal. It is apparently the reduction of the diffusible calcium that is associated with the appearance of tetany, regardless of the level of the total calcium. This is further substantiated by the fact that in nephrosis and kala-azar (9) the low total calcium which in these conditions is due to a reduction of non-diffusible calcium alone, is not accompanied by neuro-muscular irritability. When the blood calcium was raised with accompanying clinical improvement in these two cases as by cod liver oil or parathyroid extract, the rise was more marked in the diffusible than in the non-diffusible fraction, again emphasizing the prime importance of the diffusible calcium in maintaining a normal neuro-muscular irritability.

From the metabolism data presented, the comparative efficacy of the various treatments in tetany is obvious. The administration of hydrochloric acid in this form of tetany does not seem to be a rational therapeutic procedure. In case I, there was a transient increase of blood calcium with slight relief of symptoms, but a negative balance of calcium was obtained with increased excretion of calcium both in the urine and feces. With further use of the acid, the blood calcium went back to the original level with reappearance of tetany, and the calcium loss was increased. Hydrochloric acid seems to possess a depleting influence on the calcium stores of the body. Case II showed no con-

sistent response to the acid treatment. Although there was no actual calcium loss from the body, the blood calcium was slightly decreased. Thus the acid administration may or may not raise the blood calcium, and has a tendency to increase the excretion of calcium.

Merely increasing the intake of calcium did not raise the blood calcium nor relieve the symptoms in either case. Various authors attribute the failure to the lack of absorption from the intestines, but this does not seem borne out by the data presented, as the retention of calcium during the periods of calcium chloride administration is both absolutely and relatively greater than the control periods, thus showing good absorption. Apparently it is not absorption alone that controls the level of blood calcium, and there must be some other factor that keeps the absorbed calcium in the blood so as to be available for the maintenance of normal excitability of the nerves. This active factor seems to reside in both cod liver oil and parathyroid extract. The potent parathyroid extract, as these two cases exhibit, promptly increases the blood calcium to normal levels with complete relief of symptoms. There was no increased excretion of calcium either in the feces or urine, contrary to the findings of Greenwald and Gross (21) with experiments in dogs. In fact there was a tendency to increased calcium retention in both cases, especially in case II. This is in agreement with the results of Hoag et al. (26) in the treatment of two cases of infantile tetany. The prompt and marked action on the blood calcium without extensively affecting the calcium balance indicates that the main function of the parathyroid hormone seems to be the control of the distribution of calcium between the blood and tissues rather than the regulation of the rate of excretion or absorption. This substantiates the work of Stewart and Percival (23).

Cod liver oil seems to be efficacious both in raising the blood calcium and in increasing the calcium retention. In both cases, the blood calcium was promptly and markedly increased with the administration of cod liver oil. The increase in the retention of calcium was also very pronounced, more so when the calcium intake was restricted, as no further increase in calcium retention could be brought about with the aid of cod liver oil when calcium intake was already in excess, as in case II. Thus besides controlling the level of blood calcium, cod liver oil increases the positive calcium balance. Examination of the

output of calcium in urine and feces during the cod liver oil periods shows that the fecal output is greatly decreased, while the urinary output remains stationary or slightly increased, suggesting that cod liver oil acts on the intestines, either increasing the absorption or decreasing the elimination, probably the former

With regard to phosphorus metabolism the results are less regular and less conclusive. Hydrochloric acid seems to increase the retention of phosphorus, and the decreased phosphorus output is probably the result of the increased chloride available for excretion. Similarly, calcium chloride increases the phosphorus retention, though not so markedly as in the case of hydrochloric acid. Parathyroid extract gives no consistent results on the phosphorus balance, nor does cod liver oil.

The changes in the blood, other than those of calcium, are slight and inconstant.

We may add a word about the pathogenesis of the type of tetany which occurs in the orphanage concerned. The clinical features, the seasonal incidence and the favorable response to cod liver oil therapy as well as to ultra-violet radiation in case II during her first admission, justify its classification as infantile tetany. As stated in the beginning, the calcium intake in the orphanage diet is decidedly deficient, and, as shown by the metabolic data during the preliminary periods, the calcium retention is also very low. But the restricted intake and poor retention cannot be the only factors responsible for the occurrence of tetany, as the administration of large quantities of calcium fails to relieve the symptoms or raise the blood calcium, although the calcium given is absorbed and retained with avidity. There must be an additional, perhaps more important factor that regulates the distribution of calcium between the blood and tissues. Parathyroid extract is potent in this respect. But these cases do not behave as cases of tetany resulting from loss of parathyroid glands, and the peculiar seasonal variation speaks against a deficiency of parathyroid action, which would be more or less continuous.

Cod liver oil (or the active principle therein contained) is also very active in raising blood calcium, and in increasing the retention of calcium, especially when the intake is limited. But if it were a case of deficiency in cod liver oil or its active principle as is quite possible

in view of the monotonous, low-fat containing diet, the seasonal incidence again would require explanation. When the fact that the incidence of tetany varies with the intensity of the ultraviolet ray in the solar spectrum is considered, may it not be likely that the ultraviolet ray being more intense in the summer is sufficient to make up for whatever is deficient, but becomes quite ineffective in the winter? However further work seems necessary along this line.

SUMMARY AND CONCLUSIONS

1 Two of a large series of cases of tetany resembling infantile tetany occurring in an orphanage are studied with respect to the effects of various treatments on the calcium and phosphorus metabolism.

2 Merely increasing the intake of calcium does not relieve the symptoms nor raise the blood calcium, although 50 to 60 per cent of the intake may be retained.

3 Hydrochloric acid gave a transient rise of blood calcium with slight relief of symptoms in one case, but failed to do so in the other case. It tended to deplete calcium from the body stores.

4 The rise of blood calcium with relief of symptoms following parathyroid extract injections is prompt and marked. There is no increased excretion of calcium either in the urine or feces. In fact, the retention of calcium tends to increase slightly.

5 The effect of cod liver oil is similar to that of parathyroid extract, but more lasting. In addition there is a marked increase in the retention of calcium, especially when the calcium intake is limited. It seems to be the most efficient treatment in this type of tetany.

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A COMPARATIVE STUDY OF THE EFFECTS OF VARIOUS TREATMENTS ON THE CALCIUM AND PHOSPHORUS METABOLISM IN TETANY

II. CHRONIC ADULT IDIOPATHIC TETANY

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Chronic tetany in adults is usually one of two types. In the first type it is associated with loss of parathyroid glands during operations of thyroid. In the second, it occurs in individuals with lesions in the gastro intestinal tract leading to alkalosis. Cases of chronic tetany in elderly individuals unassociated with either of the above-mentioned conditions are extremely rare in the literature. The following case is recorded on this account as well as in view of metabolic data obtained that may throw some light on the pathogenesis of this type of tetany.

REPORT OF CASE

L H C, Hospital No 15810, a Chinese man of 46, unmarried, gardener by occupation, was admitted to the Peking Union Medical College Hospital on January 14, 1927, and discharged slightly improved on June 20, 1927.

Present illness The patient remained in excellent health until three years and a half before admission when he first noticed spasmodic stiffness of hands and arms, and at times of feet and legs. The spastic attacks started from the finger tips, spreading upward to the arms and shoulders, usually preceded by numbness and a prickling sensation. With severer attacks, there were slurring of speech, feeling of obstruction in the larynx and difficulty in deglutition. Each attack lasted from a few minutes to many hours, occurring with a frequency varying from several times a day to once in several days. At times the spasms were more or less continuous. Both the severity and frequency of the attacks bore no relation to season. Shortly after the onset of the spastic attacks, he began to have diarrhea, 10 to 15 stools daily, watery, with mucus, but no blood. Abdominal cramps and tenesmus were present. Since the acute attack of diarrhea, which lasted for about a month, his stools continued to be loose, once or twice daily. A year ago, he had the first attack of unconsciousness with clonic convulsions of all extremities, cyanosis, stertorous breathing and foaming in mouth. He regained consciousness

in about ten minutes. Since then, similar epileptiform fits have occurred irregularly once every few days to once in several months. The last attack, which prompted his visit to the hospital, took place two days prior to admission.

Past history He had no past illnesses that he could recollect. No operation had been performed on his neck. There was no history of tetany in early childhood, and no other members of the family were similarly affected. His diet was not essentially different from that of the laboring class to which he belongs. There was no nausea, vomiting or other gastro-intestinal disturbance in the past that would possibly suggest gastric tetany.

Physical examination This revealed a middle-aged man, well-developed and fairly well-nourished. Weight 56.9 kgm. Height 164 cm. His hands and feet were held in typical carpopedal spasm. A strongly positive Chvostek's sign was obtained. Raising the arms vertically over the head caused pain in the upper extremities (Pool's phenomenon). Besides the signs of hyperirritability of the neuro-muscular system, other neurological examinations were negative. The hair was normal, and there were no dental changes. The thyroid gland was palpable, but not enlarged. The heart and lungs were normal. Blood pressure 98/72. The abdomen was slightly distended with gas. The liver, spleen and kidneys were not palpable.

Laboratory findings Urinalysis showed no albumin, and no sugar. Indican reaction was slightly positive. Stools were semi-fluid containing ascaris and hookworm ova in small numbers. Blood examination: White blood cells 7200 with 66 per cent of polymorphonuclear neutrophils, 12 per cent of lymphocytes, 9 per cent of large mononuclears, 12 per cent of eosinophils, and 1 per cent of basophils. Blood Wassermann reaction and Kahn test were negative. Total serum calcium was 6.0 mgm per 100 cc with 2.4 mgm diffusible, and 3.2 mgm non-diffusible. Serum inorganic phosphorus was 7.21 mgm, plasma sodium chloride 550 mgm, and carbon-dioxide combining power 67.2 volumes per cent. Basal metabolism with Tissot's spirometer was +0.2 per cent. Gastric analysis showed no free acid either in the fasting content or in the specimen one hour after the Ewald's test meal. Gastro-intestinal roentgen ray examination revealed some retention of barium meal in ascending, transverse, and descending colon in 48 hours. Otherwise it was normal. Roentgenogram of pelvis showed no changes in the bones.

RESULTS

This patient was put on the same régime and studied in the same manner as the two cases reported in the first paper of this series (1). His diet was kept constant throughout the experimental period with an intake of calcium of approximately 0.35 gram daily. The results of the study are summarized in table 1 and chart 1.

The first line of treatment was parathyroid extract given subcu-

TABLE 1

Period	Date	Treatment	Intake				Output				Balance		Retention		Blood serum				Plasma		
			Urine		Stool		Total				Ca		P		Ca		P		NaCl	CO ₂	
			Ca	P	Ca	P	Ca	P	Ca	P	grams	grams	Total	Diffusible	Non-diffusible	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.			mgm. per 100 cc.
1927	1	January 19-22																			
	2	January 23-26	Parathyroid extract 60 units daily	1 3960.5	3390.0	2037.3	0540.1	2440.1	3600.1	4477.4	4140.0	-0 0517	0 9450	- 3 7	17 6	6 0	2 4	3 2	7 21	550	67 2
	3	January 27-30	Parathyroid extract 25 units daily	1 4190.5	3138.0	1223.3	4610.1	1970.1	3820.1	3193.5	0430.0	0 0997	0 2708	7 0	5 1	6 3	3 2	3 1	7 10	594	61 4
	4	January 31-February 3	Parathyroid extract 25 units daily	1 4540.5	0178.0	1136.3	1460.0	9100.1	0100.1	0236.4	1360.0	0 4304	0 8618	29 6	17 2	9 0	6 5	3 6	6 25	575	65 3
	5	February 3		1 3367.5	1024.0	3283.1	9648.0	3750.0	6533.2	5398.0	0 6834	2 5626	51 1	50 2	6 2	2 9	3 7	6 25	588	60 7	
	6	February 12-15	HCl 10 per cent 12 cc. daily	1 4296.4	6574.0	3114.2	4184.0	4937.0	6246.0	8101.3	0430.0	0 6193	1 6144	43 3	33 7						
	7	February 16-19	HCl 10 per cent 14 cc. daily	1 4440.4	3342.0	3382.2	2654.0	8367.1	1993.1	2249.3	4647.0	0 2191	0 8595	15 2	19 9	5 8	3 3	2 5	7 14	597	55 7
	8	February 20-23	HCl 10 per cent 28 cc. daily	1 4410.3	8396.0	3121.2	4496.0	9660.0	9637.1	2981.3	4153.0	0 1429	0 4443	9 9	11 5	5 2	3 1	2 5	6 67	382	65 2
	9	February 26-March 3	CaCl ₂ 2 grams daily	4 3260.3	5564.0	2737.1	8165.1	4203.0	5406.1	6940.2	3371.0	2 6320	1 1993	60 8	33 4						
	10	March 4-7	CaCl ₂ 2 grams daily	4 2975.3	4874.0	2523.2	0230.2	5345.1	1211.2	7868.3	1441.0	1 5107	0 3433	37 5	9 8	6 5	3 2	3 3	7 70	569	65 3
	11	March 8-11	CaCl ₂ 2 grams daily	4 2770.3	3934.0	2673.1	9053.1	9629.0	8964.2	2307.2	8017.0	2 0468	0 5917	47 9	17 7	6 5	2 6	3 9	8 33	569	65 3
	12	March 12-15	Cod liver oil 50 cc. daily	1 4337.3	5137.0	2399.1	7146.1	1256.0	9268.1	3665.2	6412.0	0 0672	0 8720	4 7	24 8	6 3	2 6	3 9	9 09	562	69 1
	13	March 16-19	Cod liver oil 50 cc. daily	1 4018.3	3302.0	2299.2	1213.1	4157.0	7945.0	6451.2	9158.0	-0 2433	0 4144	-17 3	12 4						
	14	March 20-23	Cod liver oil 50 cc. daily	1 4298.3	9524.0	3041.2	2637.0	8120.0	8232.1	1161.3	0919.0	0 3137	0 8603	21 9	21 8	6 5	3 3	3 2	7 14	359	69 1
	15	March 24-27		1 4227.3	4914.0	2662.1	9993.0	8767.0	7816.1	1729.2	7811.0	0 2498	0 7103	17 5	20 3						
	16	March 28-31	Kaolin 30 grams daily	1 4223.3	4244.0	3665.1	9016.1	0150.1	7863.1	3815.3	6869.0	0 0407	-0 2623	2 8	7 7	6 5	3 2	3 4	3 84	575	64 3
	17	April 1-4	Kaolin 30 grams daily	1 3747.3	3464.0	3383.2	0017.0	3559.0	6923.0	6942.2	6940.0	0 6805	0 6524	49 5	19 3	6 4	3 2	3 3	6 66	583	65 3
	18	April 5-8		1 3610.3	2772.0	3091.1	9999.0	8043.0	8791.1	1134.2	8700.0	0 2476	0 4072	18 2	12 4						
	19	April 9-12	Parathyroid extract 72 units daily	1 4145.3	5576.0	2684.2	1919.0	8715.0	8350.1	1399.3	0769.0	2 2746	0 4807	19 4	13 5	6 5	3 6	3 1	6 25	600	65 5
	20	April 13-16	CaCl ₂ 2 grams daily	4 2548.3	1728.0	3026.3	4829.1	5350.0	5448.2	0386.4	0257.0	2 2162	-0 8329	52 1	-26 9	9 6	6 8	3 1	5 00	573	66 4
	21	April 17-20	Parathyroid extract 60 units daily	4 2785.3	2358.1	4409.2	9045.1	9310.0	9362.3	3719.3	8407.0	0 9064	-0 6049	21 2	-18 7	11 1	6 6	4 6	4 35	387	70 2
	22	April 29-May 2	CaCl ₂ 2 grams daily	1 4076.3	9454.0	4136.2	1926.0	8720.0	7644.1	2856.2	9570.0	0 1220	0 9884	8 7	25 1	6 8	3 4	3 4	3 20	562	72 1
	23	May 3-6	Ultraviolet radiation (3 days only)	1 4440.4	1694.0	2961.2	1832.1	1283.0	8991.1	4246.3	0843.0	0 0194	1 0851	1 3	26 0	6 6	3 2	3 3	5 88	569	71 1
	24	May 7-10	Ultraviolet radiation	1 3376.3	5444.0	3976.1	8096.0	7152.0	6329.1	1131.2	4425.0	0 2245	1 1019	16 8	31 1	6 6	3 5	3 1	6 66	578	64 3
25	May 11-14	Ultraviolet radiation (3 days only)	1 3377.3	8252.0	2858.2	0766.0	9586.0	6233.1	1444.2	6999.0	0 1933	1 1253	14 5	29 4	6 6	3 5	3 1	8 33	375	71 1	

taneously 60 units a day for two periods of four days each. This was followed by complete disappearance of tetany with cessation of diarrhea and epigastric discomfort. His serum calcium was raised from 6.0 to 9.0 mgm, the rise being mainly in the diffusible fraction. The calcium balance, being negative during the fore-period, became positive, and increasingly so with the further administration of the extract. The blood calcium decreased to 6.2 mgm at the end of the period during which parathyroid extract was discontinued.

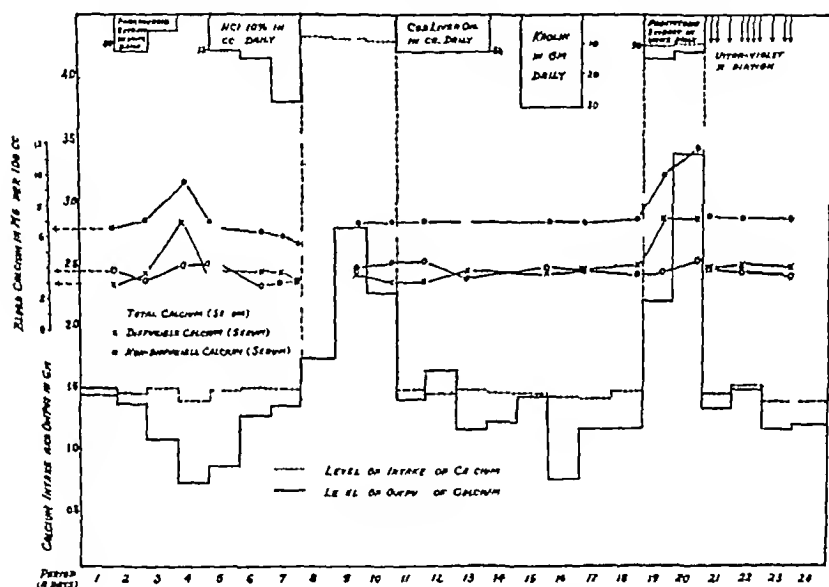


CHART 1 SHOWING THE EFFECT OF VARIOUS TREATMENTS ON THE CALCIUM BALANCE, AND THE TOTAL, DIFFUSIBLE AND NON-DIFFUSIBLE SERUM CALCIUM

Then three periods were devoted to hydrochloric acid treatment during which he experienced moderate relief of symptoms, but Chvostek's and Trousseau's signs remained marked. The blood calcium, instead of being increased, decreased from 6.5 to 5.2 mgm, the further reduction here being in the non-diffusible portion. The calcium retention was lowered from 43.3 per cent during the first period to 9.9 per cent during the third period of the acid administration, the increased excretion occurring chiefly in the stools.

During the next three periods, calcium chloride, 2 grams daily, was given, thus increasing the intake three-fold. This caused no improvement in the patient. The blood calcium remained at 6.5 mgm., in spite of the strongly positive calcium balance, 37 to 60 per cent of the intake being retained.

Cod liver oil given in 30 cc. daily doses for the next three periods again made no change in the patient's condition. His blood calcium stayed at about the same level, and the retention of calcium was not increased. In fact, during the second period of cod liver oil administration, the balance was negative.

In view of the possibility of this case being associated with intestinal intoxication, two periods were used for the oral administration of kaolin in 20 per cent suspension which might adsorb any toxins from the intestines, as suggested by the work of Braafadt (2). This was not followed, however, by any beneficial effect. The blood calcium again failed to rise. During the first period of kaolin treatment, the calcium intake and output approximately balanced each other, while the output of phosphorus was remarkably increased giving rise to a negative balance. During the second period, however, both calcium and phosphorus were fairly well retained.

After two rest periods, parathyroid extract and calcium chloride were given together for two periods, during which all signs of tetany disappeared and the blood calcium rose from 6.5 to 11.1 mgm., a level higher than normal. Here the rise of blood calcium was again more in the diffusible than in the non-diffusible fraction. During the first period of combined treatment when the blood calcium was approaching the normal level (9.6 mgm.), the calcium retention was about the same in extent as during the periods in which calcium chloride alone was given. But in the second period of combined treatment when the blood calcium (11.1 mgm.) was elevated above the normal level, markedly increased excretion of calcium occurred in the urine, giving rise to a decreased calcium retention as compared with the periods of calcium chloride alone.

Ultraviolet radiation was given a trial for the next three periods. Each exposure was made at 40 cm. distance for 5 to 15 minutes on the chest, abdomen, legs or back. There were ten exposures in twelve days of the experimental periods. There was no subjective improve-

ment noticed Neither the blood calcium, nor the retention of calcium was increased by the treatment

DISCUSSION

This is a case of chronic tetany in a man of 45, accompanied by diarrhea and epileptic fits It is not associated with operative removal of the parathyroids The absence of gastro-intestinal lesion that would lead to alkalosis, and the repeated findings of a normal bicarbonate and chloride content in the blood would exclude gastric tetany A very few possibly similar cases in women are reported in the literature, but none in men Moffitt (3) in 1911 described two cases of chronic tetany in women, aged 41 and 45 respectively, in whom neither an operation had been performed on the neck, nor a lesion in gastro-intestinal tract found Findlay and Sharpe (4) reported another case of chronic tetany in a woman of 52 with diarrhea as a pronounced feature, as in the present case Underhill, Tileston and Bogert (5) studied a similar case of tetany in a woman of 35, associated with intestinal putrefaction and foul diarrhea They found that calcium absorption proceeded normally, but the blood calcium was not raised by even a large intake of calcium Pregnancy did not enter as a factor in any of these cases

The association of epileptic attacks in this type of tetany is not known Gibson (6) reported a case of juvenile idiopathic tetany in a boy of thirteen with epileptic fits, and quoted Redlich as reporting 72 cases in which epileptic seizures accompanied or followed tetany Of them, 21 were in tetany following loss of the parathyroids, 17 in chronic juvenile cases, 5 in obstetrical cases, and the remainder in gastric and infantile tetany No mention was made of chronic adult idiopathic tetany such as existed in our case

Concerning the metabolic data obtained, the most striking feature is that none of the treatments instituted had any marked beneficial effect except the parathyroid extract, given either alone or combined with calcium chloride Cod liver oil, the effective remedy for infantile tetany and the type of tetany in adolescent girls reported in the first paper (1), failed entirely in this case There was no alleviation of symptoms, nor was there any increase in blood calcium or retention of calcium Likewise ultraviolet radiation proved inadequate

Kaolin was also ineffective. There was an increased retention of calcium when the calcium intake was raised, but no relief of symptoms nor rise of blood calcium. Hydrochloric acid induced only slight improvement in the spastic attacks, but the resultant lowering of the blood calcium and decrease of calcium balance indicate that the administration of hydrochloric acid is not a desirable treatment.

The effect of parathyroid extract in this case is unique in that it completely relieved the symptoms and signs of tetany as well as the intestinal disturbance coincidently with the prompt and marked rise of blood calcium, especially of the diffusible calcium. When the blood calcium was raised nearly to normal, there was a slight increase in calcium retention, but when it rose above normal, the excretion of calcium in the urine was increased. The variation in calcium excretion correlated with the blood calcium level probably accounts for some of the discrepancies in the reports by various authors regarding the effect of the parathyroid extract on the excretion of calcium.

The failure to obtain results with other treatments than parathyroid extract in this case suggests the existence of a primary parathyroid deficiency with resulting disorder of calcium metabolism, hyperirritability of the neuro muscular system and intestinal disturbances. Such a deficiency can only be remedied by supplying the normal hormone of the parathyroid glands which is supposedly contained in the extract. Swingle and Rhinhold (7) in the treatment of ten parathyroidectomized dogs with ultraviolet radiation found that this did not prevent tetany nor the fall of blood calcium. Similarly Jones (8) failed in his treatment of parathyroidectomized dogs with cod liver oil. The lack of response to either cod liver oil or ultraviolet radiation in the case presented, as in these dogs with actual loss of the parathyroids, would also lend support to the hypothesis that this case represents one of parathyroid deficiency.

SUMMARY AND CONCLUSIONS

An unusual case of chronic tetany in a Chinese male of 46, unassociated with alkalosis or removal of the parathyroids is reported. Epileptic fits and intestinal disturbances were accompanying features. Of all the treatments instituted only parathyroid extract gave relief of symptoms and elevation of blood calcium. When the blood calcium

approached normal, there was an increased retention of calcium, but when it rose above normal a decreased retention occurred. Cod liver oil, ultraviolet radiation, kaolin, calcium chloride, and hydrochloric acid were all ineffective. The lack of response to all other treatments except the parathyroid extract is taken to indicate a probable primary parathyroid deficiency as the cause of tetany in this case.

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GASTRIC ACIDITY RELATION TO VARIOUS FACTORS SUCH AS AGE AND PHYSICAL FITNESS

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In previous papers we reported the results of studies of gastric function carried out by means of a standard alcohol test meal (1). The work had two objectives—first, to investigate the diagnostic value of “gastric analysis” and second, to obtain information about certain questions of physiology of the stomach. The present report deals with the relations of gastric acidity to various factors such as age and physical fitness.

Ever since the introduction of test meals as a means of studying the function of the stomach, clinicians have been interested in estimating the acidity of the gastric juice. Certain outstanding facts were soon discovered. It was found, for example, that the degree of acidity varied in different people, and that gastric ulcer was often associated with high acidity, whereas in cancer of the stomach there was absence of “free HCl.” The exact diagnostic significance of gastric acidity has, however, never been accurately defined, some observers regard high acidity (hyperacidity) and anacidity as distinct diseases or disorders, while another view is that great variations may exist without any pathological significance.

It seems evident that some of this uncertainty is due to a lack of accurate information about the normal variations of acid secretion, which will be discussed below.

METHODS

A miscellaneous group of 90 people was studied. Although they were hospital patients many of them were, to all intents and purposes, normal. Others suffered from various disorders, but no one with

demonstrable organic disease of the stomach, such as cancer, ulcer or pernicious anemia, was included. Desperately ill and moribund patients were also excluded. The acidity of the gastric juice, following stimulation with a standard alcohol test meal, was determined. The procedure has been described in detail (1) and curves of acid secretion have been published (2). In the following charts titratable acidity is expressed in terms of the number of cubic centimeters of $N/10$ NaOH necessary to neutralize 100 cc of gastric juice, phenolphthalein was used as indicator. It should be specially emphasized that the values herewith presented refer to the highest acidity of the pure gastric juice attained after stimulation. These values are obtained by making allowance for dilution of the gastric juice by the test meal (1). Values from direct titration of test meal specimens are often incorrect and misleading, owing to various errors which have been pointed out elsewhere (2).

RESULTS

Range of acidity in people without disease of the stomach

In the present group, titratable acidity of the pure gastric juice varied from 0¹ to 118. The percentage distribution of the cases according to height of acidity (exclusive of those having an anacidity) is shown in chart 1. Over 40 per cent of the subjects had an acidity between 60 and 80, and 60 per cent of the estimations fell between the limits of 50 and 90. There was no evidence, however, that the people with values of under 50 or over 90 had any disease of the stomach.

In no person, either normal or with gastric disease, have we ever encountered an acidity over 135. This is in harmony with the observations of others that there is a definite upper limit of acidity which the human stomach can, under no circumstances (3), exceed. The value corresponds approximately to 0.5 per cent HCl.

To obtain further information on this point histamine was employed. The effect of this substance on gastric secretion has been discussed previously (4), suffice it is to say that it acts as a powerful stimulus. People without gastric disease, who showed various degrees of acidity after the alcohol stimulus, were selected, 0.5 mgm

¹ Acidity is recorded as 0 when the pH was above 3.0

of histamine was then injected subcutaneously and the test was repeated. The results are shown in table 1.

TABLE 1
Titratable acidity before and after histamine

Case number	Diagnosis	Titratable acidity before histamine	Titratable acidity after histamine
		cc. 0.1 N per 100 cc. pH 6.3	cc. 0.1 N per 100 cc. pH 3.4
27	Cancer of liver	0	0
5	Mitral stenosis	0	13
69	Normal	0	67
43	Normal	13	33
15	Hyperthyroidism	16	34
65	Normal	43	65
61	Normal	50	134
284	Normal	91	112
13	Normal	81	124

50 PERCENT or GROUP

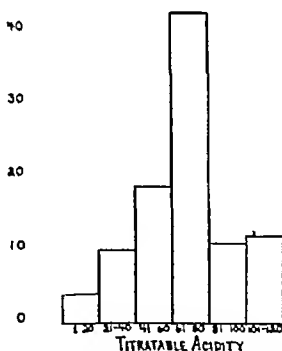


CHART 1 PERCENTAGE DISTRIBUTION OF ALL CASES ACCORDING TO DEGREE OF GASTRIC ACIDITY

In every case a juice of greater acidity was secreted after histamine. The degree of increase did not, however, bear a constant relation to the value obtained before histamine was given, and the acidity never

exceeded the upper limit which has previously been mentioned. It is evident then, that the acidity of the gastric juice is in no sense a physiological constant to be compared, for example, with the reaction of the blood. Why one person secretes a more acid juice than another is not at present known, the point of practical importance is that a very liberal interpretation must be put on acid values in the diagnosis of clinical disorders, and that acidities over the entire range, from 0 to approximately 130, are compatible with health and with the absence of demonstrable disease of the stomach.

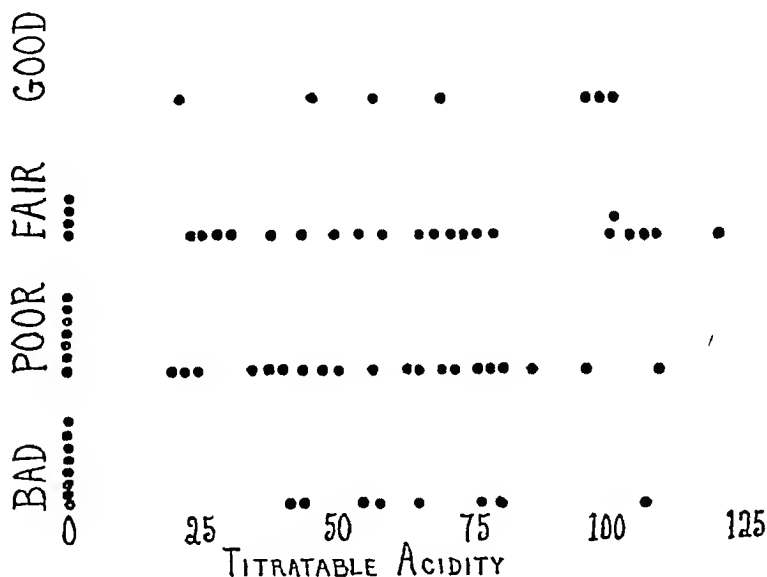


CHART 2 RELATION OF GASTRIC ACIDITY TO PHYSICAL FITNESS

Relation of gastric acidity to physical fitness

One wonders, naturally, whether a person's general state of health and well being, apart from disease of the stomach, bears any relation to the degree of acidity of the gastric secretion. Baird, Campbell and Hern (5) have studied this question, and they found no clear relation between degree of acidity and physical fitness. However, they dealt with a group of healthy young adults, who were all well, even though some were of superior physique. The subjects of the present study, on the other hand, represented all degrees of physical condition in a

miscellaneous group of people who had in common only the fact that there was no demonstrable organic disease of the stomach. Our grouping as to fitness is purely arbitrary; the subjects are divided into four groups (good, fair, poor, bad) depending on our impression of their general physical status. A robust young man with a local lower urinary tract lesion is classed as "good," a patient with cancer of the liver and cachexia is classed as "bad," etc. The results of the

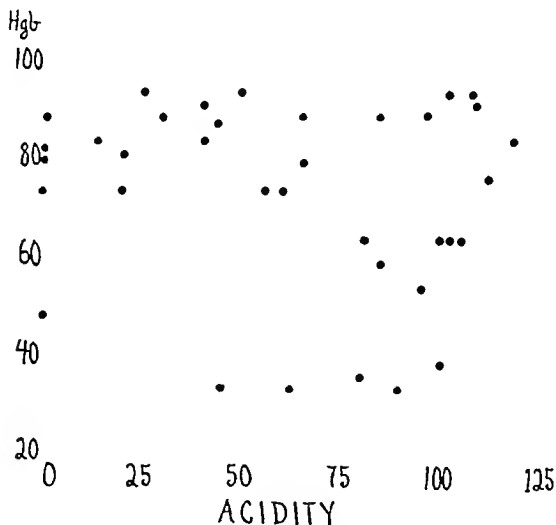


CHART 3 RELATION OF GASTRIC ACIDITY TO HEMOGLOBIN

inquiry are shown in chart 2. Each dot represents the highest acidity reached, after the alcohol meal, in a different person. Values from zero up to 100 or more were found in all groups, although more than half of the patients whose physical condition was classed as "bad" had an anacidity. The average acidity of the "good" and "fair" groups combined was 69 and of the "poor" and "bad" 33, so that there appears to be a definite relationship between fitness and

acidity However, other factors, such as age, enter into the question and the matter will be discussed below more in detail

AGE

80

70

60

50

40

30

20

10

TITRATABLE ACIDITY

CHART 4 RELATION OF GASTRIC ACIDITY TO AGE

Anemia

The relationship of anacidity to pernicious anemia is definitely established, whether lack of blood in itself is associated with defective gastric secretion, is not definitely known In chart 3 are shown

some observations in cases other than pernicious anemia. Degree of acidity is plotted against per cent of hemoglobin. Unfortunately we have only a few observations in very anemic patients, but as far

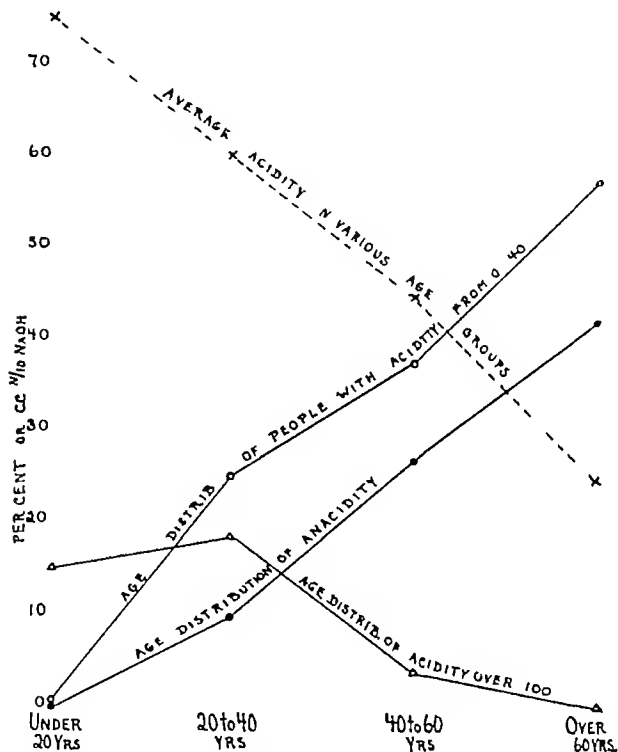


CHART 5 RELATION OF GASTRIC ACIDITY TO AGE

as they go they give no indication that anemia, *per se*, is responsible for lack of gastric secretion. More observations are being made on this point.

Age

Various observers have shown that gastric secretion is not fully established at birth, and according to Marriott and Davidson (6), and Davison (7), relatively few infants secrete enough HCl to give the red reaction with dimethyl amido-azobenzene. Between the ages of 15 and 20 years, however, abundant acid is usually present although even among young people approximately 5 per cent fail to show free HCl, when tested with the fractional gruel meal. With advancing years the frequency of "anacidity" increases, and Keefer and Bloomfield (8) found in a large group of people without evidence of any anatomical disease that anacidity (Ewald test meal) was present in over 20 per cent of people in the 50--60 year age period and in over

TABLE 2
Relation of age and physical fitness to acidity

	All cases	Good	Bad
All cases	Average titratable acidity→	58	29
	↓		
Under 30	65	77	48
Over 50	38	38	16

thirty-five per cent of those beyond 60 years. Dedichen (9) made similar observations. It is not clear, however, from the literature whether the increased frequency of anacidity in old people is merely an expression of a general lessening of secretion of acid in all people as they grow older or whether special causes operate at this time of life to produce deficiency of acid in particular individuals without everyone being affected.

In the present study the highest acidity reached in each case after the alcohol meal was plotted against the age of the subject. The results are shown in chart 4.

At first glance one is struck by the scattering of the dots, which shows that at any age period there is a wide variation in acidity in different people. However, the increasing frequency of anacidity with advancing years is evident, as well as the decrease in high acidities (90 or over). When the average acidity in various age periods is

charted, a striking general decrease with advancing years is noted. That this is not due merely to more instances of anacidity (chart 5) is shown by charting on the same scale the per cent of the total group with acidities of less than 40 and over 100. These observations suggest the possibility that as the individual grows older his gastric secretion tends to become less acid. If his acidity at the age of 20 was 100 it might, for example, be only 60 at the age of 65, if it was 40 in youth there might be an anacidity in old age. In considering the

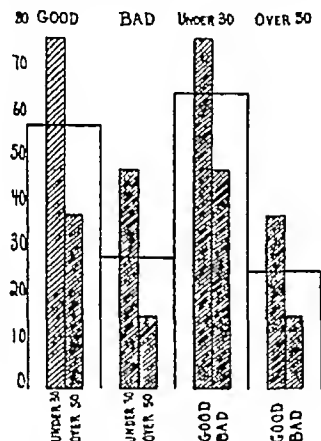


CHART 6 RELATION OF AGE AND PHYSICAL FITNESS TO ACIDITY

relationship of gastric acidity to disease it is therefore necessary to take age into account. This point has already been stressed in relation to anacidity, but is brought out more clearly by the present observations.

In order to be sure that the apparent relation of gastric acidity to age was genuine and was not modified by physical fitness, the figures were analyzed from another point of view. A series of cases was selected in which general physical condition was definitely good or bad. These were further divided into young (under 30 years) and old

(over 50 years) Both factors were then correlated with average acidity in the various groups The results are shown in table 2 and chart 6 Physical condition seems clearly related to degree of gastric acidity, but age as far as the present observations go, is a more important factor

SUMMARY

A study has been made of the acidity of the (undiluted) gastric juice after a constant stimulus in a miscellaneous group of patients, none of whom, however, had organic disease of the stomach The values varied over a wide range but on the whole could be correlated with two factors—age and physical fitness The former seems the most important, and our observations indicate that as people grow older they tend to secrete a less acid gastric juice No attempt is made at present to explain the mechanism of the deficiency

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GASTRIC MOTILITY AND THE VOLUME OF GASTRIC SECRETION IN MAN

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(Received for publication July 18, 1927)

In a previous paper (1) we discussed the relation of degree of gastric acidity of people without organic disease of the stomach to physical fitness, age, and other factors. It was shown that acidity tends to decrease with advancing years and that people in poor general physical condition, on the whole, have a less acid stomach juice than those who are fit. The present report deals with a similar study of the volume of gastric secretion and gastric motility after a standard stimulus.

METHODS

The subjects were part of the group used for the previous observations (1). As far as possible organic lesions of the stomach were excluded in every case. The tests were carried out by the method which has previously been described in detail (1, 2).

The volume of gastric secretion

In a previous paper (3) it was pointed out that following stimulation of the stomach with 50 cc. of 7 per cent alcohol the maximum ten minute volume of gastric secretion varied in different people from 10 to 40 cc. with occasional greater or smaller values. The present larger series of 51 people is in essential agreement since all but four observations fall within the range of 10 to 50 cc.

Relation of volume of secretion to age

In view of the clear relationship of gastric acidity to age, an inquiry was made as to the relation of age to volume of gastric secretion. The dots in chart 1 indicate the highest ten minute secretion volumes, after the standard alcohol stimulus, in different cases plotted in rela-

tion to the age of the subjects. The tendency to lower volumes in older people is obvious and is shown graphically in chart 2. The explanation of this phenomenon is not yet clear.

Relation of volume of secretion to physical fitness

It was found that gastric acidity was diminished in people whose physical condition was poor. No such clear relationship could be demonstrated in the present series with regard to volume of secretion.

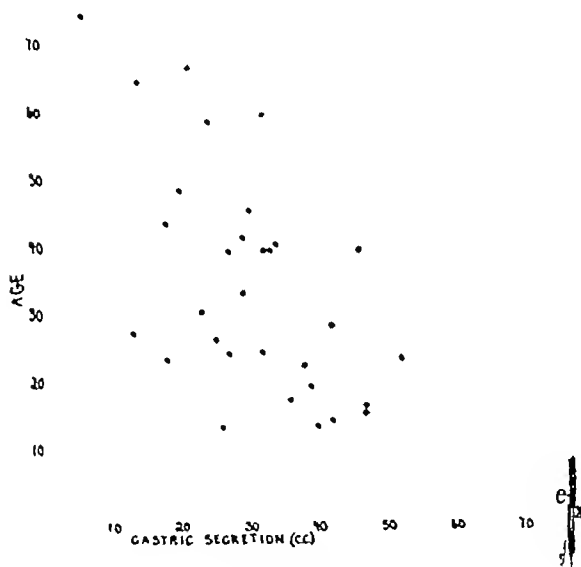


CHART 1

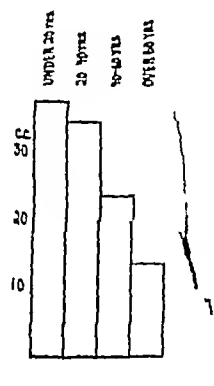


CHART 2

CHART 1 RELATION OF VOLUME OF GASTRIC SECRETION TO AGE

CHART 2 RELATION OF VOLUME OF GASTRIC SECRETION TO AGE

The average maximum ten-minute volume of those in good condition was 33.5 cc, of those in bad condition 27 cc. That these figures were not due to accidental age distribution in the two groups is shown by the following analysis (table 1).

Gastric motility

The question of gastric motility may be discussed from either of two aspects. First, there are the considerations of pure physiology

which deal with the complex phenomena of the contractions of the stomach and with the analysis of the neuromuscular mechanisms which are involved. Secondly, there is the clinical problem of the diagnostic significance of gastric motility. Radiologists and clinicians have placed a good deal of stress on "retention" beyond a certain length of time, "spasm," "hypermotility" and "atony," but the exact interpretation of gastric motility in disease, apart from definite pyloric obstruction, is still very uncertain. The present observations have little, if any, theoretical importance, they deal simply with an objective study of the volume of contents and the emptying time of the stomach under controlled conditions after a standard stimulus. Our object was to obtain, if possible, a base line with which the findings in instances of gastric disease could be compared.

TABLE 1
Relation of age and physical condition to volume of gastric secretion

	All cases	Good condition	Bad condition
	"	"	"
All cases		33 5	27
Under 30 years	33	41 0	37
Over 50 years	20	20 0	19

The procedure, as previously described, consisted of introducing into the empty stomach through a small tube 50 cc. of 7 per cent alcohol. The subjects were all in bed under "basal" conditions. At ten-minute intervals the entire stomach contents were aspirated through the tube, which remained in place throughout the experiment. A sample of 10 cc. was retained at each aspiration and the remainder was immediately re-injected into the stomach. It was possible, therefore, to plot curves showing the volume of stomach contents at regular intervals. Such volumes, needless to say, represent the sum of the fluid introduced and the gastric secretions, less contents which have escaped through the pylorus. A few curves were published in a previous paper (3) but a much larger series (consecutive cases) is now presented.

It is at once apparent that the curves (chart 3) have an orderly character, two different types can be distinguished. In the first group,

following the introduction of the alcohol there is a steady increase in gastric content which reaches a maximum in from 30 to 50 minutes

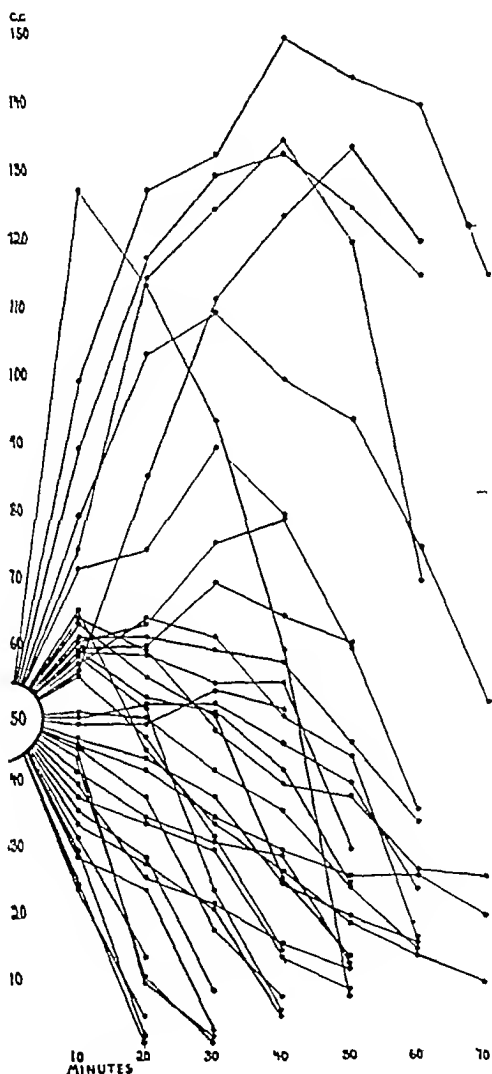


CHART 3 VOLUME CURVES OF GASTRIC CONTENTS

and then declines, often rapidly, in the second group the volumes decrease from the start. In a few cases the curve is intermediate between the other two types. It is of interest that the regularity of

the curve does not seem to be interfered with by the frequent aspirations, in no instance, for example, does the curve rise after once beginning to fall. It is evident that under the conditions of these experiments a regular and orderly action of the stomach is revealed, the rising curves, of course, indicate predominance of gastric secretion over discharge the falling curves indicate the reverse, although

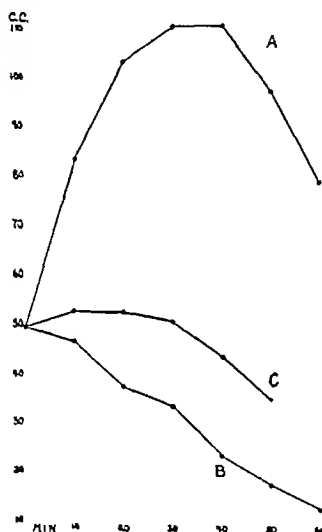


CHART 4 COMPOSITE VOLUME CURVES OF GASTRIC CONTENTS

neither type gives any direct information as to volume of gastric secretion. We have found, however, that the high curves are usually associated with large volumes of secretion, the falling curves may or may not have such significance. Chart 4 (C) is a composite graph of the averages of all the curves shown in chart 3. A is a composite of all the curves with initial rise and B of all the curves with an initial fall.

Emptying time of stomach

Chart 3 also shows the emptying time in various cases. The great variation is apparent, in some cases the stomach was empty in 20

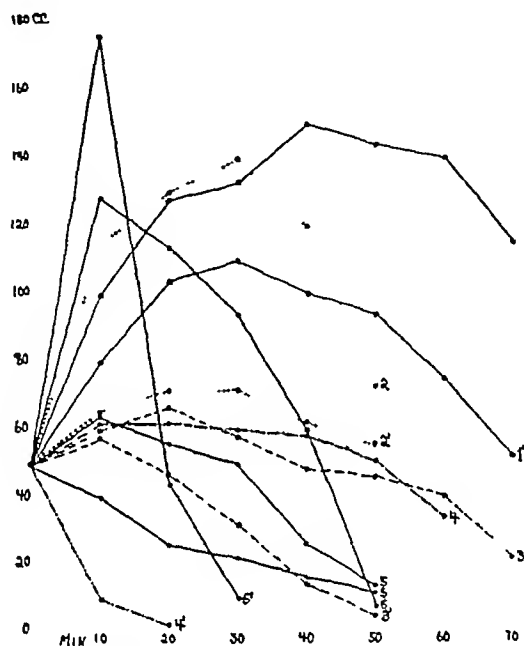


CHART 5 REPEATED VOLUME CURVES OF GASTRIC CONTENT

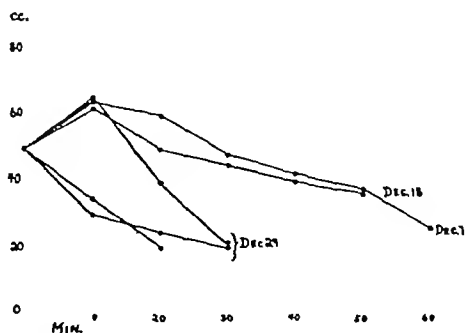


CHART 6 REPEATED VOLUME CURVES IN ONE PATIENT

minutes, in others there was still a large quantity of gastric contents at the end of an hour or more. In view of the orderly character of

the curves, we tried to find out if the type of curve was characteristic of a particular stomach. Repeated observations were therefore made in a number of cases and the graphs are shown in chart 5. In our previous paper (3, 4) we stressed the great variations in the motility of the stomach on successive examinations. While this fact is quite correct there is none the less a striking general similarity between most of the curves obtained on successive occasions in the same subject. Six pairs of curves are shown in chart 5. Each pair represents the first examination and a second one made after an interval of a week or more. Curves 4 and 4' are the only ones which show any extreme difference. We have repeated observations in 15 cases, in 12 the curves were similar. Chart 6 shows curves from five examinations of the same person. In all a good deal of similarity is apparent although the speed of emptying varies.

SUMMARY

The present observations have been made with a view to establishing the volume of secretion and the gastric volume curve after a uniform stimulus in order to set standards with which observations in instances of gastric disease can be compared.

In addition to defining the normal variations in volume of gastric secretion it is pointed out that volume of secretion as well as acidity decrease with advancing years. Curves of volume of total gastric content are presented and discussed.

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A COMPARATIVE STUDY OF THE ROTATORY AND REDUCING PROPERTIES OF PLASMA ULTRAFILTRATES FROM DIABETIC AND NEPHRITIC PATIENTS

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(Received for publication August 5 1927)

In a previous paper (1) a method for studying the rotatory values present in human blood plasma has been discussed, and a series of comparative reducing and rotatory values have been presented, recording the values obtained from normal individuals and hospital patients, exclusive of diabetics and nephritics. It was found in this series that the rotatory values of plasma ultrafiltrates, if expressed in terms of glucose generally proved to be lower than the reducing values and in fact, good agreement between the two was recorded in only a few instances. These recognized differences between the reducing and rotatory values were designated in the experiments as R-P values (the reducing minus the polariscopic value) and, in the previous series, were found to range between the equivalent of 0 and 0.130 gram of glucose per 100 cc., averaging about 0.040 gram per 100 cc. The rotatory values proved to be somewhat irregular, however, for in studying the ultrafiltrates over a period of seventy-two hours, fluctuations were noted, amounting to an average value of ± 0.022 gram of glucose, whereas the reducing values remained practically unchanged. These findings conform in general to those which have been reported by other investigators whose work has been reviewed in the previous communication.

At the outset, however, it is well to re-emphasize the fact that studies of the R-P values of blood plasma consist essentially in the measurement of a rather complex property of human blood plasma and not

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in the measurement of a substance. Furthermore we are dealing with a property which under the given conditions is in all probability somewhat labile and may be subject to mutarotatory phenomena and may be quite sensitive to certain environmental conditions, such as temperature, the hydrogen ion concentration, the presence of oxidizing or reducing agents, etc. Attention has been called to this fact by other workers in this field who have also pointed out that if we assume that the reducing power and the specific rotation of glucose in the blood is the same as that of an aqueous solution of α,β -glucose in equilibrium, the differences then between the rotatory and reducing values expressed in terms of glucose may be due either to the presence of reducing substances other than glucose, or to the presence of optically active substances other than glucose without giving a clue as to the nature of either type of substances. As a matter of fact both explanations seem to be in part responsible for the R-P values. In the case of the former it is recognized that small amounts of reducing substances which cannot be attributed to glucose may be present in blood. The exact nature of these substances has not been defined, although it is known that creatinine, creatine, uric acid, glycuronic acid, pentoses, disaccharides, purines and adrenalin have the power of reducing the reagents commonly used in blood sugar determinations, and, after the removal of glucose from blood by yeast fermentation or by the glycolytic action of whole blood, the residue of reducing substance has been found to be equivalent to 0.010 to 0.030 gram of glucose per 100 cc. (2). In the case of the other optically active substances it has been suggested that they may be represented by β -oxybutyric acid, amino acids and glycuronic acid (3), or by non-protein sulphur compounds (4) (5), all of which are known to exist in the blood. The quantitative data on this subject are as yet too limited to warrant a very profitable discussion as to their nature.

In extending the work in an effort to determine the nature and significance of these R-P values the number of determinations on clinical cases has been increased in the present study, for the immediate purpose of determining whether these values would show any degree of uniformity if classified according to the type of disease. Although the number of cases which are reported below is small, the findings show that in at least two types of disease, namely, in diabetic and in

nephritic patients with uremia, a certain degree of uniformity has been observed

It is not within the scope of this paper to explain the general nature of the factors producing these differences between the reducing and rotatory power of the blood but rather to call attention to the values obtained. In the nephritic series, however, a note is made of an obvious factor which has been shown to be in part responsible for the differences

Although there have been a number of studies in which comparisons between the rotatory and reducing values are recorded, the number of observations of this type, which have been made upon groups of pathological cases appears to be limited

Stepp (6) has reported a series of such determinations expressed in terms of glucose, upon a group of seventeen normal individuals, a group of fourteen diabetics in which some of the cases exhibited evidences of acidosis, a group of six nephritic cases both with and without nitrogen retention, and a small group of five miscellaneous cases. This author worked with blood filtrates from which the protein had been precipitated with phosphotungstic acid and which had been subsequently concentrated by vacuum distillation

In his original filtrates he reported large differences between the high reducing and the low rotatory values, his attention being largely confined to a discussion of the factors which promote these differences. He considered however, that the rotatory values were a more accurate index of the true blood sugar content than the reducing values owing to the very appreciable presence of reducing substances other than glucose which could be removed by mere vacuum distillation or by the addition of neutral lead acetate. Although his observations do not easily lend themselves to an analysis such as the one given below, no appreciable degree of uniformity in the reducing rotatory difference is detectable in any of the particular groups of cases which he studied.

A somewhat similar study of the differences between rotatory and reducing values in the blood of normal individuals and in diabetics has been reported by Winter and Smith (7). They found that after precipitating the blood protein and concentrating the filtrate in vacuo the rotatory values of normal blood filtrates, expressed as above, were considerably below the reducing values, but on standing, these rotatory values rose until in a day or two they had become equivalent to the latter. In diabetic individuals, however the differences in rotatory and reducing values with a subsequent rise of the former were not observed.

Lundsgaard and Holbøll (8) have also studied the differences between the rotatory and reducing power in dialyzates obtained from normal and diabetic blood and have reported findings which show the same general trend as those observed by Winter and Smith.

METHODS

The procedure, including the methods of obtaining the blood and filtering it through collodion sacs, which has been followed in the present study has been practically the same as that outlined in the previous communication (1). A slightly different technique was, however, employed in about half of the observations given below for the polariscopic determinations. The 189 mm polariscope tube with a Mazda lamp and an appropriate dichromate solution filter as the source of light were replaced by a longer tube and a mercury vapor lamp using the green light with an arc of low pressure. A special polariscope tube measuring 241.8 mm in length and holding 10 cc of solution was constructed for this purpose, which utilized the maximum length allowed by the instrument and at the same time did not require the use of an excess of solution. The length of the tube was also gauged to facilitate the calculations for estimating the per cent of glucose which is derived by the well known formula

$$\text{Per cent of glucose} = \frac{\text{Reading} \times 100}{\text{Specific Rotation} \times \text{length of the tube in dm}}$$

By employing a wave length of 5461 Å, the specific rotation of glucose is 62.03° (9) giving the final calculation

$$\text{Per cent of glucose} = \frac{\text{Reading} \times 100}{62.03 \times 2.418} = \frac{\text{Reading}}{1.5}$$

In determining the error by the use of this method readings were made upon a series of standard glucose solutions of a concentration of approximately 0.100 per cent. The readings on the solutions were frequently alternated with readings of the zero point. The average error of each individual determination actually proved to be about the same as that previously reported amounting approximately to ± 0.010 gram of glucose, although theoretically the increased length of the tube should increase the accuracy of the method.

The reducing determinations were run by the method of Folin and Wu (10).

In the previous communication, attention was called to the fact that the rotatory values observed in the plasma ultrafiltrates frequently showed fluctuations from day to day. These fluctuations represent an uncontrolled variable in our hands, but in order to attain a moderate degree of uniformity the rotatory readings, upon which the calculations in this study have been based, were in all instances made on the day following that on which the sample of blood was obtained and filtered.

All averages are followed by the standard deviation of the average calculated by the formula

$$\sigma = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$$

where σ = standard deviation

x = an observation

\bar{x} = the average

n = number of observations in the average

No averages have been considered as significantly different unless they differ by more than the sum of their standard deviations or by the square root of the sum of the squares of their standard deviations.

EXPERIMENTAL

Normals

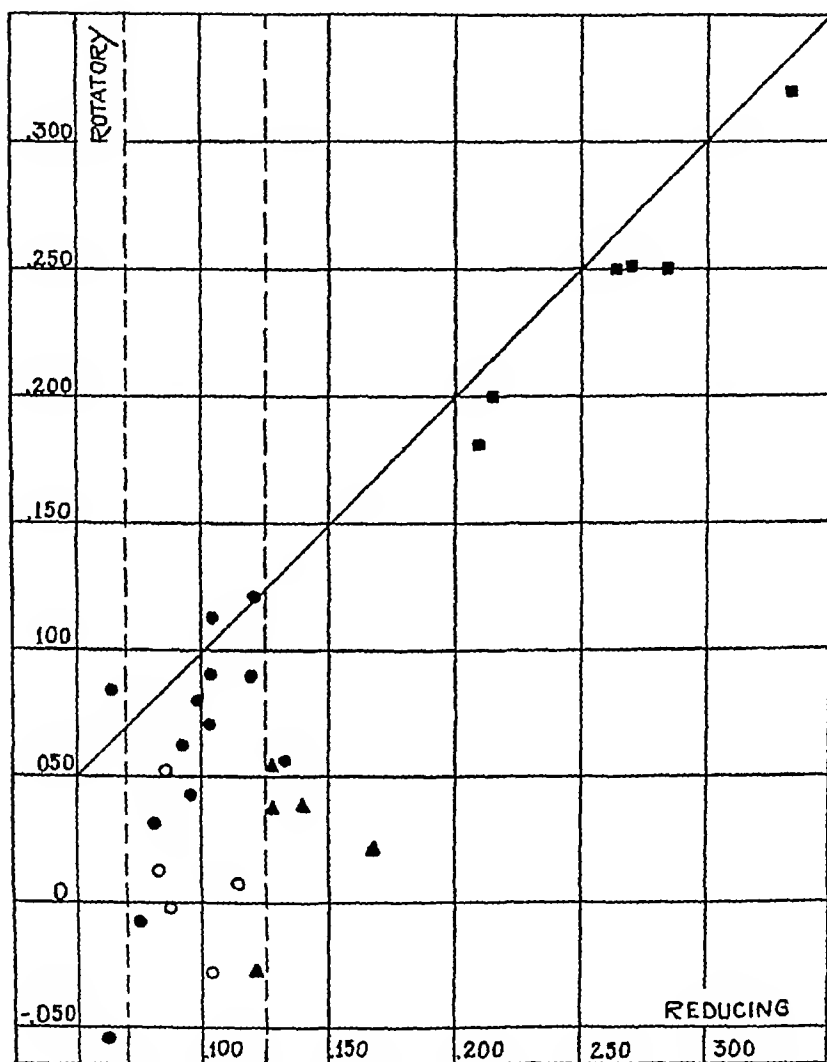
The results of a small series of reducing and rotatory determinations with the corresponding differences between the two, expressed in

TABLE 1
Ultrafiltrate reducing and rotatory values obtained in 5 normal individuals

Number	Diagnosis	Reducing value	24-hour rotatory value	R P
37	Normal	0 085*	+0 051	0 034
38	Normal	0 109	+0 007	0 102
40	Normal	0 086	-0 003	0 089
41	Normal	0 104	-0 028	0 132
42	Normal	0 032	+0 013	0 069
Minimum R P value				0 034
Maximum R P value				0 132
Mean R P value				0 085 \pm 0 036

* All of the reducing and rotatory values in this and subsequent tables are expressed as grams of glucose per 100 cc.

terms of glucose as R-P values, which have been made upon a series of five adult normal individuals are shown in table 1. It will be noted that the rotatory values are appreciably below the reducing values in all five instances and the resulting R-P values are large varying from 0 034 to 0 132 gram per 100 cc., and averaging $0 089 \pm 0 036$. These values are also graphically presented in figure 1, in which the rotatory values have been plotted against the reducing ones. It will be seen that the points all fall within a relatively small area, which is within the range of normal fasting blood sugar values. The relatively large R-P values are emphasized by the chart.



○ Normals ● Miscellaneous Cases ■ Diabetics ▲ Nephritics

FIG 1 THE DISTRIBUTION OF THE ROTATORY AND REDUCING VALUES FROM A SERIES OF BLOOD SAMPLES OBTAINED FROM NORMAL INDIVIDUALS, MISCELLANEOUS CASES, DIABETICS AND NEPHRITICS

The oblique line indicates the position of the points of exact agreement between reducing and rotatory values. The limits of usual normal fasting "blood sugar" or reducing values, are marked by the two vertical broken lines.

Miscellaneous cases

The reducing and rotatory values obtained from a group of thirteen miscellaneous cases which represent a variety of clinical conditions are shown in table 2 and graphically in figure 1. Three of the rotatory values are actually larger than the reducing ones resulting in negative R-P values. In general, the R-P values range from a minimum of -0.021 to a maximum of 0.116 with an average value of 0.031 ± 0.037 . Although the points shown in figure 1 cover a rather wide area, they fall for the most part within the range of normal fasting blood sugar values. A striking feature of the cases with higher reducing values is

TABLE 2

Ultrafiltrate reducing and rotatory values obtained in 12 miscellaneous hospital cases

Number	Diagnosis	Reducing value	24-hour rotatory value	R P
51	Arteriosclerosis	0.102	+0.115	-0.013
52	Arteriosclerosis	0.064	+0.085	-0.021
35	Pyelitis	0.092	+0.063	0.029
27	Cardiac decompensation	0.102	+0.071	-0.031
43	Cardiac decompensation	0.134	+0.105	0.029
62	Cardiac decompensation	0.061	-0.055	0.116
26	Lobar pneumonia, syphilis	0.102	+0.091	0.011
64	Lobar pneumonia	0.071	+0.031	0.040
74	Rheumatic fever	0.119	+0.090	0.029
28	Salvarian poisoning	0.095	+0.041	0.054
20	Cirrhosis of liver	0.075	-0.008	0.083
67	Pyonephrosis, syphilis	0.118	+0.120	-0.002
68	Pyonephrosis	0.097	+0.080	0.017
Minimum R P value				-0.021
Maximum R P value				0.116
Mean R P value				0.031 \pm 0.037

that the majority of them give rotatory values showing a close degree of approximation to the reducing values, a feature which will be subsequently shown to be quite characteristic of the diabetic series. This fact was so noticeable that the attempt was made to determine whether the group of individuals in which these small R-P values were recorded showed any common clinical features. Unfortunately, the amount of data which had been collected on these patients was small and our information is limited, but it seemed to be a noticeable feature

that all of the R-P values which were below 0.030 in this series occurred in patients who were showing evidence of vascular disease either syphilitic or arteriosclerotic. However, too many variables enter the problem to allow stressing this point which seems rather to be a feature warranting further investigation.

Diabetic cases

All of the diabetic specimens were obtained from ambulatory patients who were attending the Diabetic Clinic of the Out Patient Department of the Pennsylvania Hospital.² The values obtained in six of these diabetic patients are recorded in table 3, also in figure 1 by the points represented as small squares. It will be noted that the

TABLE 3
Ultrafiltrate reducing and rotatory values obtained from 6 diabetic cases

Number	Diagnosis	Reducing value	24-hour rotatory value	R P
A	Diabetes (insulin treatment)	0.264	+0.250	0.014
B	Diabetes	0.208	+0.179	0.029
C	Diabetes	0.333	+0.320	0.013
53	Diabetes (insulin treatment)	0.270	+0.251	0.019
56	Diabetes (insulin treatment)	0.284	+0.248	0.036
60	Diabetes	0.214	+0.197	0.017
Mean R-P value.				0.021 \pm 0.009

specimens were obtained during stages of moderate hyperglycemia in which the reducing values range from 0.214 to 0.333. The consistently close approximation which the rotatory values bear to the reducing values is a striking feature of this series. The R-P values are uniformly small, averaging 0.021 ± 0.009 mgm per 100 cc. The distribution of the points in relation to the line of equality between rotatory and reducing values is emphasized by figure 1.

This finding of the close approximation between rotatory and reducing values in diabetics has been previously noted by Winter and Smith (7) and Lundsgaard and Holbøll (8). Considerable literature has arisen with regard to its significance. It is not the purpose of this article to discuss the significance of the finding but merely to call

²I am indebted to Dr. E. S. Dillon for the privilege of studying these patients.

attention to our confirmation of it, noting at the same time that some fairly low R-P values are also recorded in some of the miscellaneous, non-diabetic patients. It would seem therefore, that low R-P values, although characteristic of the diabetic series, do not represent a finding which is specific for that disease.

Chronic nephritis with uremia

Early in the course of this study it was noted that large R-P values were encountered in nephritic cases with uremia and consequently a small series of these cases was assembled for further study. This type of case, namely that of advanced chronic nephritis of arterio-

TABLE 4

Reducing and rotatory values obtained from patients with chronic nephritis (nephrosclerosis) and uremia

Number	Initials	Date	Plasma urea nitrogen	Plasma creatinine	Reducing value	Rotatory value	R P
			mgm. per 100 cc	mgm per 100 cc			
29	A. R	April 20, 1926	179	25	0.140	+0.038	0.102
30	A. D	April 27 1926	277	20	0.121	-0.028	0.149
31	A. D	April 28 1926	277	20	0.168	+0.021	0.147
69	M. N	May 20, 1927	150	16	0.127	+0.055	0.072
76	L. L	July 6 1927	210	16	0.127	+0.038	0.089
Minimum R P value							0.072
Maximum R P value							0.149
Mean R P value							0.112 \pm 0.035

sclerotic origin (nephrosclerosis) was selected for investigation because the findings proved to be relatively consistent and because we were dealing with a clearly defined clinical entity, in which we succeeded in confirming the diagnosis at necropsy in all of the cases recorded. Furthermore the degree of intensity as evidenced by blood urea nitrogen and creatinine determinations could be easily followed. The studies were made during the stages of terminal uremia.

The results of this series of observations are recorded in table 4, and the points have also been charted as small triangles in figure 1. It will be noted that the R-P values tend to be large, ranging from 0.072 to 0.149 and averaging 0.112 ± 0.035 . In figure 1 the points

fall in a group which does not coincide exactly with the points registered by the control cases, due in some measure to the fact that the reducing figures occupy a higher range than the controls and also to the fact that the R-P values tend to be large

The distribution of these points which have been obtained from the nephritic cases, suggests that reducing substances other than glucose may be more responsible for the increased R-P values in this group than in the others. The increase in the reducing power of the blood in cases with nitrogen retention is recognized. It has been shown to be partly due to the presence of reducing substances such as uric acid and creatinine which are present in increased amounts. Hiller, Linder and Van Slyke (2) have found that, after submitting normal blood to yeast fermentation or to the glycolytic action of whole blood, the residue of reducing substance other than glucose was equivalent to 0.010 to 0.030 per cent of glucose. They showed that in a series of five cases of chronic glomerulonephritis with nitrogen retention, four showed abnormally high amounts of total reducing substance and the non-glycolyzable residual reducing substances were increased to about the slight extent that might be expected from the retained uric acid and creatinine, most of the total reduction values being from 0.020 to 0.050 per cent. These authors noted, however, that the important part of the increase in reducing substances in the nephritic cases was due to material which when fermented or incubated lost its reducing power as does glucose.

As the observations just mentioned apparently have a very definite relationship to the R-P values, we have also determined the amounts of non-fermentable reducing substances in the ultrafiltrates from some of our nephritic cases.

The experiments were performed in the following manner. The reducing and rotatory values were first determined. To about 25 cc. of ultrafiltrate a small portion (about a fifth) of yeast cake was added, the suspension was agitated and placed in the incubator at 37° for one hour. The suspension was then refiltered through a collodion membrane and its reducing and rotatory value redetermined.

The results of a small series of such determinations on a filtrate of ox blood and on three filtrates from human nephritic blood are shown in table 5. It will be noted that the values obtained from the non-

fermentable residue are uniformly lower than those reported by Hiller, Linder and Van Slyke, but it is evident none the less, that they show an appreciable relationship to the creatinine content and that reducing substances which include creatinine and uric acid are probably responsible for a definite fraction of the large R-P values encountered in the nephritic cases

It will also be noted that the R-P values after fermentation are less than those reported before fermentation. The factors tending to produce this latter phenomenon are unexplained and are in contrast to the results obtained after removal of sugar by the glycolytic action of whole blood where it has been shown that subsequent to this procedure the R-P values were increased (1)

TABLE 5

Rotatory and reducing values on animal and nephritic blood before and after fermentation

Number	Before fermentation				After fermentation			
	Creatinine	R	P	R P	Creatinine	R	P	R P
Ox	1.8	0.127	+0.031	0.096	1.7	0.011	-0.040	0.051
A	9.2	0.184	+0.090	0.094		0.015	-0.060	0.075
B	17.0	0.083	-0.100	0.183		0.026	-0.130	0.156
C	19.8	0.048	-0.132	0.180	16.8	0.029	-0.085	0.114

Although it is a rough estimate it is noteworthy that if we assume that a maximum value of 0.030 will cover the average non fermentable fraction of reducing substances in the uremic bloods we still obtain an average R-P value, which is far larger than the average value obtained in the series of miscellaneous cases. Interestingly enough, however, the average nephritic values minus 0.030 approximates the average R-P value obtained in the normal series

Post mortem samples of blood

Owing to the occasional clinical difficulty of obtaining the large quantities of blood necessary for these determinations, a number of blood samples were secured quite soon (i.e., within two hours) after death and the reducing rotatory determinations were compared with the series of ante-mortem figures. It is to be emphasized at the start, however, that a comparison of post mortem analyses of this type with

the figures obtained during life should be made with caution as a variety of factors have to be considered which generally do not concern us in the interpretation of ante-mortem values. After death, the stabilizing influences which normally control not only blood volume, but its reaction, the non-protein nitrogen, the chloride content and a host of other substances, break down with considerable rapidity together with the appearance of autolytic phenomena. This breakdown does not necessarily await the death of the patient for it is recognized that the conditions of the terminal hours are often not comparable with those of ordinary life and during these terminal hours or even days a variety of protective and other mechanisms of the body may begin to fail.

The findings in this series of determinations proved to be fairly consistent and somewhat noteworthy. The reducing determinations were frequently found to be well below the range of normal fasting blood sugar values. The rotatory values showed still lower figures and a large per cent of them proved to be markedly levorotatory producing a corresponding increase in many of the R-P values (0.029 to 0.234). These values may be partially explained on the basis of glucose loss from the blood which we know occurs in varying degree at about the time of death (11). However, a notable feature of these observations proved to be that low reducing values were almost invariably associated with high R-P values.

In conclusion I wish to express my appreciation to Dr J. H. Austin for his helpful criticism during the course of the experiments and to Miss E. F. Herr and Mr S. L. Wright, Jr for their assistance in the analytical work.

SUMMARY

A comparative series of the reducing and rotatory values as determined upon plasma ultrafiltrates have been recorded on a group of miscellaneous cases, a group of diabetics, and a group of patients with chronic nephritis and uremia. The differences between reduction and rotation have been expressed in these observations in terms of glucose as R-P values (i.e., the reducing minus the polariscopic values) and the range of these R-P values from blood taken ante-mortem has been found to be from -0.021 to 0.149 .

It has been shown in the group of normal individuals that the R-P values are moderately high (0.034 to 0.132). In the miscellaneous cases the R-P values cover a wide range (-0.021 to 0.116) although most of them are low. On the basis of a clinical classification it has also been shown that the two distinct groups of cases chosen for study, give a series of R-P values which are characteristically different for the two groups. In the group of ambulatory diabetic patients the R-P values proved to be uniformly low (0.013 to 0.036), a fact to which attention has been called by previous investigators (7) (8). In the group of uremic patients the R-P values tend to be high (0.072 to 0.149). This increase has been shown to be in part due to the accumulation in the plasma of increased amounts of reducing substances other than glucose such as creatinine, etc. However, the findings although different for the two groups are not specific, and values which are equivalent to those observed in some of the diabetic and in some of the nephritic patients are also recorded among the normal and miscellaneous cases.

It has been further shown that both levorotation and the R-P values are increased in the blood after death, a phenomenon which is frequently associated with low reducing values.

As a general rule, however, the antemortem R-P values have been found to deviate from the normal range more frequently in those cases in which the blood sugar or reducing values are outside the usual range. Furthermore, two distinct factors have been noted in these experiments as being correlated with abnormally high R-P values. One of these is the presence in the blood of an excess of reducing substance other than glucose, and the other is the presence of an associated hypoglycemia.

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STUDIES ON THE EFFECT OF CARDIAC IRREGULARITY ON THE CIRCULATION

I THE RELATION OF PULSE DEFICIT TO RATE OF BLOOD FLOW IN DOGS SUBJECT TO ARTIFICIAL AURICULAR FIBRIL- LATION AND TO REGULAR TACHYCARDIA

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In preceding papers (1, 2) we have reported observations concerning the effect of regular and irregular tachycardia (auricular fibrillation) on the rate of blood flow in normal unanesthetized dogs

The terms "rate of blood flow" and "relative blood flow" have been used in these investigations (1, 2) to denote specific functions The *rate of blood flow* refers to the arterio venous difference in oxygen The difference corresponds to the tissue utilization of this gas The volume of gas which the tissues take depends of course on the volume of blood which passes them If their requirements (that is to say, metabolism) remain constant, the amount of oxygen taken must remain constant, provided that the volume of the blood and the partial pressure of the gases in it, also remain constant We infer that if the arterio-venous difference changes, either by increase or by diminution, the volume of blood which passes the tissues must have changed, for there is no reason to believe that there has been change in any of the other possible factors Obviously, the data do not permit definitive inferences to be drawn on the cardiac output, for we lack knowledge in these experiments of the amount of oxygen which has been breathed We have taken in a given animal, the arterio venous difference to represent 100, when the mechanism of his heart beat is normal We have also estimated it under the conditions developed by various abnormal rhythms and have found a ratio between the normal and the abnormal figures This ratio we call *relative blood flow* If, for

instance, the arterio-venous oxygen difference is 1.5 mM during a normal period and increases to 3.0 mM during an artificial rhythm, the rate of flow during the artificial rhythm must have been slower during the second period. The ratio between the two then is 1.5/3.0 or 50 per cent.

It was found that the rate of blood flow was uniformly decreased in auricular fibrillation. In regular tachycardia, on the other hand, the rate of blood flow was unchanged in two-thirds of the observations, but in one-third it was decreased. Why the rate of blood flow was unchanged in some dogs during regular tachycardia and decreased in others was not evident from the data which we had. On reflection, it appeared that the difference is not due to absolute increase in heart rate for we have increased the regular rate to 390 per minute without changing the rate of blood flow, while on other occasions a decrease occurred during rates of 250 to 280 per minute. Nor does it seem to be due to the percentile increase in rate. For instance, an increase of 50 per cent was followed by a decrease in rate of blood flow, while an increase of 129 per cent occurred without any change, that is to say an increase of 50 per cent or 100 per cent may leave the blood flow unchanged or bring about a decrease (2). The difference may, of course, lie in differences in the hearts themselves, for the response of one heart to approximately the same stimuli is not always the same as that of another. Such differences cannot, however, now be detected by measurement. It occurred to us that the presence of ineffective beats (the pulse deficit) might be one of the factors concerned in bringing about a change in the rate of blood flow which has been found in our experiments. This factor occurred to us as a possibility because we are already familiar with its occurrence in rapid auricular fibrillation in patients. We have therefore correlated in a series of experiments the rate of blood flow with the pulse deficit in regular and irregular tachycardia in the same dog. These experiments form the subject of this paper.

METHODS

The operative procedure used in the preparation of the dogs and the method of investigation were described in preceding papers (1, 2). Briefly, wire electrodes were sutured to the right auricles. The operations were performed with sterile

precautions The dogs were anesthetized with ether given by the intratracheal method After the dogs recovered from the preliminary operation the heart was stimulated through these electrodes and the effect of the new rhythm on the rate of blood flow was studied. Irregular tachycardia (auricular fibrillation) was brought about by means of a faradic current Regular tachycardias were maintained by means of single induced break shocks thrown into the auricle at a regular rapid rate, which could be varied as desired The apparatus which we used to obtain these stimuli was described in a previous paper (2) In order to calculate the pulse deficit we have recorded simultaneously on the same film the electrocardiogram and a tracing of the femoral pulse The femoral pulse was transmitted by rubber tubing from a rubber cuff applied to the right hind leg through the Kolls and Kubie modifications of the Erlanger capsule (3, 4) to a Frank capsule placed in front of the camera The rubber cuff on the leg was inflated with air to a pressure near the diastolic level The movements of a beam of light focused on the mirror glued to the membrane of the Frank capsule were reflected to the lens of the camera and were traced on the moving sensitive film.

The oxygen content of four samples of arterial and of mixed venous blood (5, 6) was estimated by the Van Slyke and Neill manometric method (7) and the relative blood flow calculated The first samples were taken during the period of normal rhythm, the second, after auricular fibrillation had been present for one hour and while it was still present, the third one to two hours after the return to the normal rhythm, and the fourth, one hour after the onset of regular tachycardia maintained artificially near the same ventricular rate as that found during the fibrillatory period The pulse deficits were calculated from simultaneous electrocardiograms and femoral pulse tracings taken at the time the blood samples were drawn In some animals the observations were made first during regular tachycardia while in others first during the period of fibrillation, but a rest period of one to two hours intervened between the two sets of observations in order to avoid confusion from the effect of the two mechanisms on the blood flow As before, the dogs lay quietly on the table without anesthesia and were so far as we know in a basal metabolic state on the day of the experiment. Under these conditions we have, as has been said, interpreted changes in the oxygen consumed per liter of blood (that is to say, the difference between the oxygen content of the arterial and of the mixed venous blood) as representing changes in rate of blood flow and not to changes in metabolism And the ratio of the oxygen consumed in the two periods gives therefore the relative blood flow We did not attempt to estimate the oxygen absorption of the dogs because of the wide variation in results obtained in untrained, unanesthetized dogs The basal oxygen consumption of an untrained dog presumably does not differ from that of the same dog lying in the same position after training The untrained dog, however reacts to the procedure used in measuring the oxygen consumption by emotional disturbances with attendant changes in oxygen consumption, while one trained to those procedures is not disturbed by them We have estimated the oxygen consumption in a few trained

TABLE 1
The correlation of rate of blood flow and pulse deficit in auricular fibrillation in dogs

Dog number	Weight kgm	Time with reference to stimulation	O ₂ content		Arterio- venous oxygen differ- ence*	Blood flow percent of initial	De- crease of blood flow percent	O ₂ capacity mM	O ₂ saturation†		Rhythm‡	Dura- tion of stimu- lation minutes	Heart rate (electro- cardio- gram) per minute	Femoral pulse rate per minute	Pulse deficit per minute	Dura- tion of rest after stimu- lation hours
			Arterial	Mixed venous					Arterial	Mixed venous						
1	14.7	Before	11.15	7.91	3.24	100		12.08	91.5	65.1	N R †	60	230	230	0	2½
		During	10.68	6.64	4.04	80	20	11.81	90.0	56.0	A. F §		240	240	50	
		After	10.72	6.03	4.69	69	31	11.59	91.7	51.7	A. F ¶		310	240	70	
2	17.3	Before	10.94	7.82	3.12	100		12.67	85.6	61.4	N R	60	150	150	0	2
		During	11.61	7.59	4.02	78	22	12.65	91.0	59.6	A. F		200-170	200-170	140-180	
		After	12.16	8.18	3.98	79	21	12.62	95.6	64.5	N R		150	150	0	
3	13.5	Before	12.38	9.52	2.86	100		12.94	95.0	73.2	N R	60	180	180	0	1½
		During	12.71	7.92	4.79	59	41	13.38	94.3	58.8	A. F		300	165	135	
		After	12.53	8.38	4.15	69	31	13.03	95.5	64.0	N R		180	180	0	
4	14.8	Before	11.25	8.17	2.99	100		11.81	94.5	77.3	N R	60	190	190	0	
		During	11.80	6.72	5.08	59	41	12.04	97.2	55.5	A. F		160-150	160-150	180-200	
		After	10.47	7.14	3.33	100		9.76 A** 9.84 V	100.0	72.2	N R		230	230	0	
5	13.9	Before	10.47	7.14	3.33	100		9.76 A** 9.84 V	100.0	72.2	N R	60	230	230	0	
		During	10.56	5.29	5.27	63	37	10.75	97.4	49.8	A. F		190	190	150	
6	10.2	Before	11.10	8.36	2.74	100		11.21	98.2	74.2	N R	60	140	140	0	
		During	11.21	6.84	4.37	62	38	11.40	97.5	59.6	A. F		210	210	130	
		After	9.57	5.88	3.69	100		9.35	100.0	62.4	N R	60	80	80	0	
7	13.5	Before	9.84	5.12	4.72	78		9.76	100.0	52.0	A. F	60	340	160	180	
		During	9.84	5.12	4.72	78	22	9.76	100.0	52.0	A. F		340	160	180	

8	11 0	Before During	11 09 11 70	8 84 6 77	2 25 4 93	100 46	54	11 88 11 90	92 6 97 5	74 0 56 5	N R. A. F.	60	160 300	160 180	0 120
9	10 5	Before During	9 00 8 67	5 91 4 19	3 09 4 48	100 69	31	9 53 9 00	93 5 95 3	61 5 46 1	N R. A. F.	60	140 320	140 200	0 120
10	12 2	Before During	10 09 10 14	6 49 4 89	3 60 5 25	100 68	32	10 83 10 55	92 3 95 3	59 5 45 9	N R. A. F.	60	170 330	170 190	0 140

* Oxygen removed from each liter of blood.

† Before calculating the oxygen saturations, 0.09 mM and 0.04 mM O_2 (the amounts of oxygen in physical solution) were subtracted from the arterial and mixed venous oxygen contents respectively

‡ N R. = normal rhythm.

§ A F = auricular fibrillation.

¶ Spontaneous auricular fibrillation was still present 2½ hours after faradic stimulation had been discontinued

** A = arterial blood, V = mixed venous blood

TABLE 2
The correlation of rate of blood flow and pulse deficit in regular and irregular tachycardia (auricular fibrillation) in dogs

Dog number	Weight kgm	Time with reference to stimulation	O ₂ content		Arterio-venous oxygen difference*	Blood flow per cent of initial	Change in blood flow†	O ₂ capacity	O ₂ saturation‡		Rhythm	Duration of stimulation minutes	Heart rate (electrocardiogram)	Femoral pulse rate	Pulse deficit	Duration of rest after stimulation hours
			Arterial	Mixed venous					Arterial	Mixed venous						
11	10 6	Before	10 59	7 05	3 54	100		10 80	97 1	64 9	N R §	60	100	100	0	2½
		During	10 69	8 34	2 35	150	+50	11 12	95 3	74 6	A N R ¶		170††	170	0	
		Before	10 62	8 16	2 46	100		11 18	94 2	72 6	N R	60	120	120	0	
		During	10 90	7 40	3 50	70	-30	11 08	97 5	66 4	A F**		300	140	160	
12	13 5	Before	8 30	6 63	1 67	100		9 23	89 0	71 4	N R		150	150	0	2
		During	8 06	6 27	1 79	93	-7	8 78	90 7	71 0	A N R	60	310†† 340	310 340	0 0	
		Before	7 98	6 25	1 73	100		8 70	90 7	71 3	N R		160	160	0	
		During	7 30	4 51	2 79	62	-38	8 14	88 7	55 0	A I	60	280 300 270	280 220 230	0 80 40	
13	18 6	Before	12 48	8 44	4 04	100		12 76	97 1	65 8	N R	60	140	140	0	2½
		During	12 34	7 90	4 44	90	-10	13 09	93 6	60 0	A N R		330	330	0	
		Before	12 48	9 00	3 48	100		12 81	96 7	69 9	N R	60	180	180	0	
		During	12 38	7 22	5 16	67	-33	13 35	92 0	53 7	A I		300	180	120	
14	14 9	Before	11 14	7 34	3 80	100		12 10	91 3	60 3	N R		170	170	0	
		During	11 12	7 25	3 87	98	-2	11 69	94 4	61 7	A N R	60	170 170 170	170 170 170	0 0 0	
		Before	11 14	7 34	3 80	100		12 10	91 3	60 3	N R		170	170	0	
		During	11 12	7 25	3 87	98	-2	11 69	94 4	61 7	A N R	60	370 370 370	370 370 370	0 0 0	

dogs during these experiments and found that the metabolism of the dogs remains constant (8) The calculations designated relative blood flow made in this paper and the two preceding ones (1, 2) are therefore valid, in so far as the assumption is made that the changes which were observed depend on changes in the rate of blood flow and not on changes in the rate of metabolism

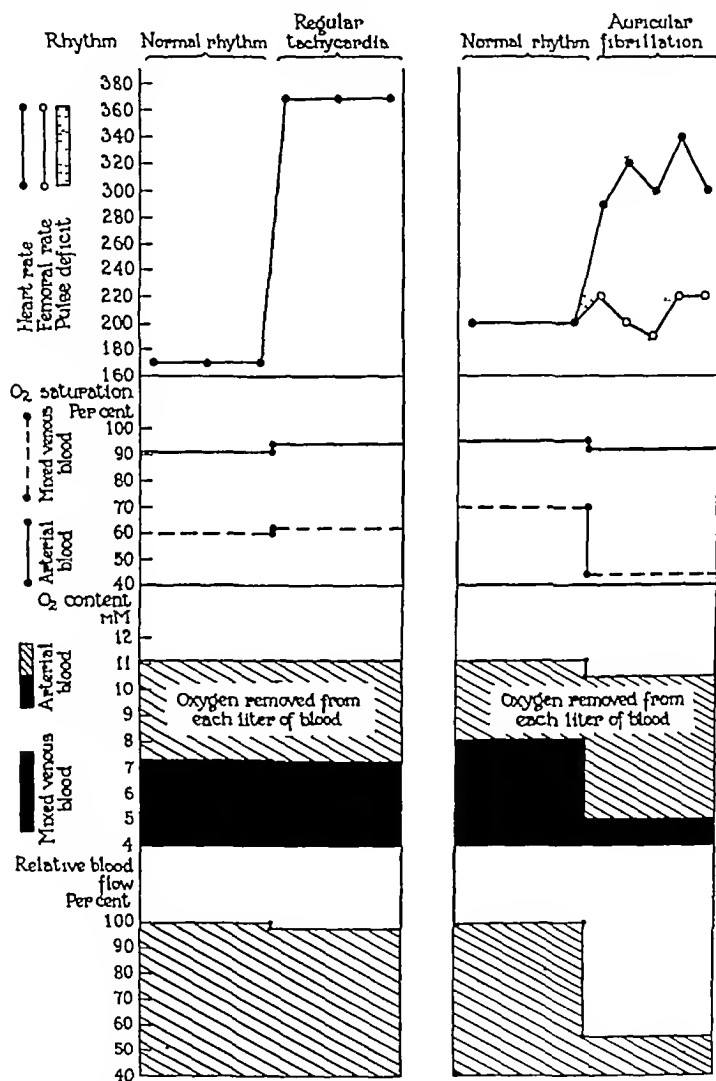


FIG 1 IN THIS FIGURE IS COMPARED THE EFFECT OF REGULAR AND OF IRREGULAR TACHYCARDIA UPON THE RATE OF BLOOD FLOW AND THE OCCURRENCE OF THE PULSE DEFICIT IN DOG 14

OBSERVATIONS

The correlation of the rate of blood flow and pulse deficit in auricular fibrillation

There are 10 sets of observations on 10 dogs (table 1) In all there was a decrease in rate of blood flow ranging from 20 to 54 per cent during the fibrillatory period During the natural normal rhythm all the beats were effective, but during the period of auricular fibrillation there were pulse deficits ranging between 50 and 200 per minute, the ventricular rates ranging between 290 and 350 per minute.

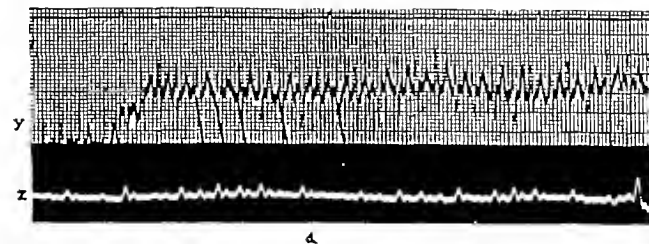
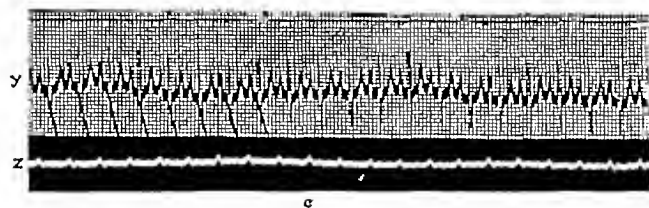
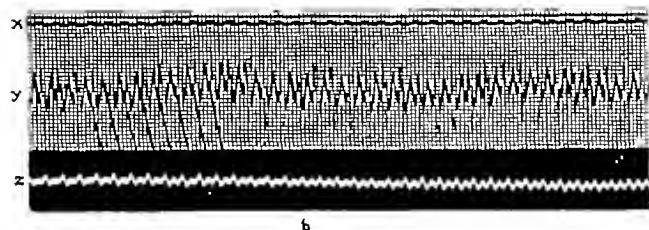
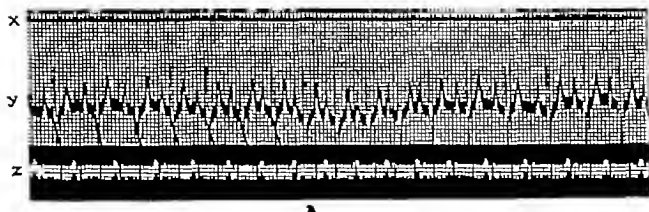
A comparison of the effect of auricular fibrillation and regular tachycardia in the same dog

In 6 dogs we have observations on the rate of blood flow and the pulse deficit during regular tachycardia as well as during auricular fibrillation (table 2) The rate of blood flow in dog 14 was unchanged during the regular tachycardia, there was no pulse deficit even when the heart was beating at a rate of 370 per minute (fig 1) During auricular fibrillation the rate of blood flow was decreased 45 per cent but there was a pulse deficit of 70 to 120 per minute, the ventricular rate varying between 290 and 340 per minute The rhythms which obtained at the time the blood samples were taken in this dog were recorded electrocardiographically with simultaneous tracings of the femoral pulse (fig 2) Similar results were obtained in 4 (dogs 11, 12, 13 and 14) of the 6 dogs

In dog 15 there was a decrease in rate of blood flow of 44 per cent during auricular fibrillation, the ventricular rate being 360 to 380 per minute, there was a pulse deficit of 180 per minute (fig 3) During regular tachycardia at the same ventricular rate (350 per minute) the rate of blood flow was, however, likewise *decreased* (22 per cent) The unexpected decrease may be explained by the fact that at times all the beats were effective, while at other times only every other beat, that is to say, there was a pulse deficit of 175 per minute The rhythms which were present at the time the blood samples were drawn were recorded electrocardiographically and simultaneous femoral

FIG 2 ELECTROCARDIOGRAMS (LEAD II) OF DOG 14 ARE SHOWN AT THE TIME THE BLOOD SAMPLES WERE DRAWN

a was taken during the normal rhythm, *b* during regular tachycardia, *c* 2 hours after the end of the period of regular tachycardia and before auricular fibrillation was started, and *d* during auricular fibrillation. In this figure as well as in figures 4 and 5, *X* is the shadow of the electromagnetic signal and shows the frequency of the induced break shocks, *Y* is the electrocardiogram, *Z* is the femoral pulse tracing. A short time interval is seen between the beginning of the QRS complex of the electrocardiogram and the corresponding femoral pulse. This is due partly to the transmission time from the heart to the femoral artery and partly to the transmission time from the rubber cuff to the Frank capsule. In the femoral pulse tracing taken during auricular fibrillation (*d* curve *Z*) attention is called to the variation in the excursion of the femoral pulse from beat to beat. In this figure and in figures 4 and 5 divisions of the ordinates equal 10^{-4} volts, divisions of the abscissae equal 0.04 of a second. The original curves are sharply contrasted black and white, no half tones are lost by the method of reproduction. The curves are reduced to two-thirds of their natural size.



d
FIG 2

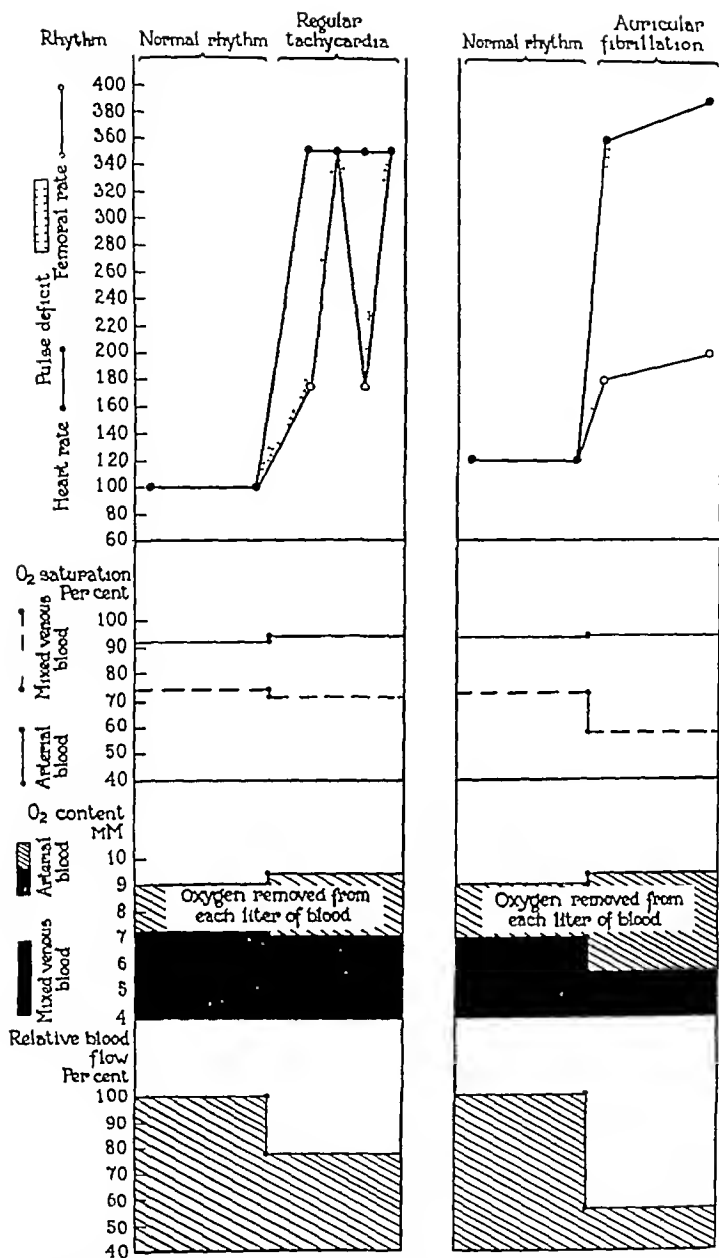


FIG 3 IN THIS FIGURE IS COMPARED THE EFFECT OF REGULAR AND OF IRREGULAR TACHYCARDIA UPON THE RATE OF BLOOD FLOW AND THE OCCURRENCE OF THE PULSE DEFICIT IN DOG 15

FIG 4 ELECTROCARDIOGRAMS (LEAD II) ARE SHOWN OBTAINED FROM DOG 15

a was made during the normal rhythm, *b* and *c* during the regular tachycardia, *d* 2½ hours after the end of the period of regular tachycardia and before auricular fibrillation was induced, and *e* at the end of the fibrillatory period. The reversion to the normal rhythm is shown. In curve *b* a pulse deficit occurs at every other beat, but in curve *c* all the ventricular beats are effective. The curves are reduced to two-thirds of their natural size.

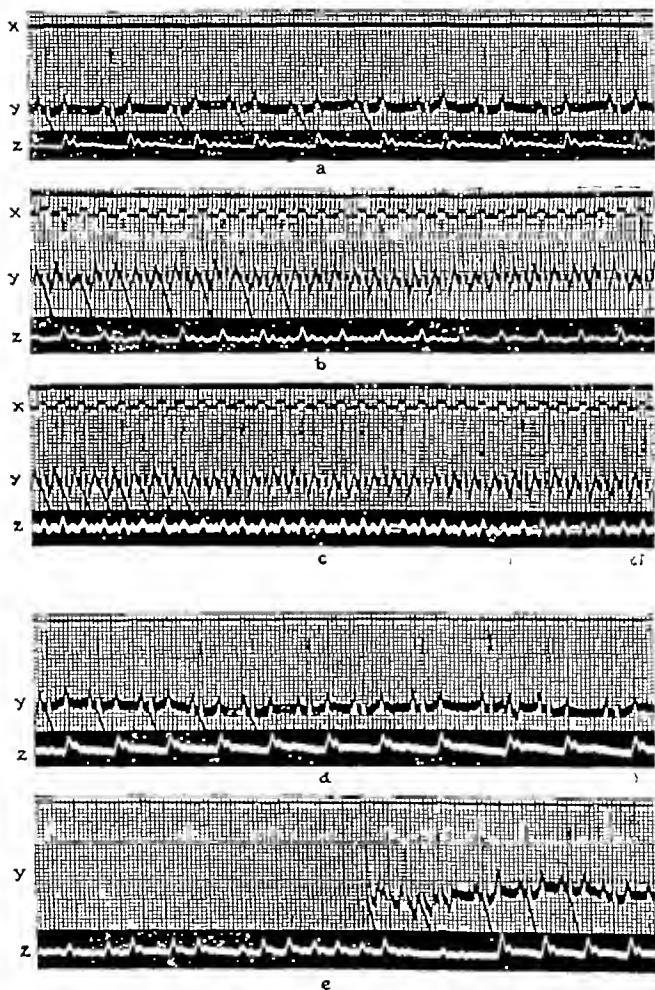


FIG 4

pulse tracings made (fig 4) A similar state was found to exist in the case of dog 16

In 6 dogs, therefore, there was a decrease in rate of blood flow during auricular fibrillation and a pulse deficit was present in each instance

TABLE 3
Summary of experiments correlating rhythm, pulse deficit and rate of blood flow

Dog number	Rhythm		Rate of blood flow			Pulse deficit	
	Rapid regular	Auricular fibrillation	Increase	No change	Decrease	Present	Absent
11 {	+	+	+		+	+	0
12 {	+	+		+	+	+	0
13 {	+	+		+	+	+	0
14 {	+	+		+	+	+	0
15 {	+	+			+	+	
16 {	+	+			+	+	
1		+			+	+	
2		+			+	+	
3		+			+	+	
4		+			+	+	
5		+			+	+	
6		+			+	+	
7		+			+	+	
8		+			+	+	
9		+			+	+	
10		+			+	+	

In 4 of these the rate of blood flow was *unchanged* during regular tachycardia and there was no pulse deficit In the other two the rate of blood flow was decreased during this rhythm but a pulse deficit occurred In short then, whenever the rate of blood flow decreased

in these experiments, whether in regular or irregular rhythms, a pulse deficit occurred (table 3)

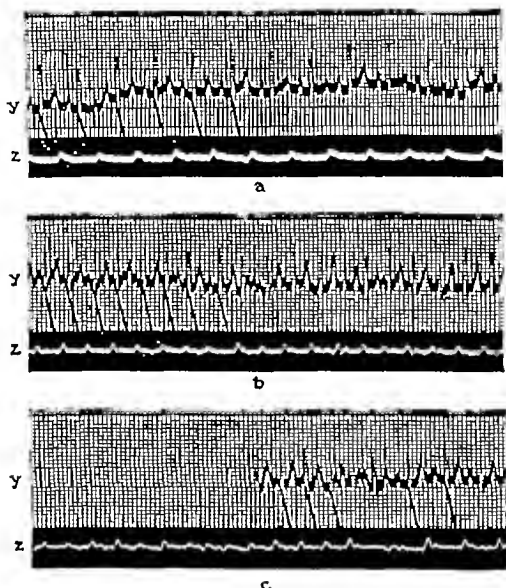


FIG 5 ELECTROCARDIOGRAMS (LEAD II) ARE SHOWN OBTAINED FROM DOG 12

a was made during the normal rhythm, *b* during auricular fibrillation and *c* at the end of the fibrillatory period. The return to the normal rhythm is shown. In curve *b* all of the ventricular beats are effective while in *c* and other portions of the record there is an occasional pulse deficit. The curves are reduced to two-thirds of their natural size.

DISCUSSION

We have shown in these experiments that whenever a decrease in rate of blood flow occurred a pulse deficit was found to be present. The pulse deficit cannot, however, be the only factor involved, for in many instances when it was found, the number of beats which were

effective was still as large as during the normal slower rate. In dog 12 for instance (table 2, fig 5) all the beats were effective in long stretches of the record, while here and there only a small pulse deficit occurred. We have no explanation to offer for this phenomenon, that is to say, the effectiveness of a certain number of beats at certain times and the ineffectiveness of the same number at others. In other cases not only were some beats wholly ineffective but there was also a variation in the degree of effectiveness of individual beats, as observed in differences in the excision of the femoral pulse from beat to beat (figs 2, 4 and 5). The inference which we draw on the nature of the influence of pulse deficit on rate of blood flow is that the intra-ventricular pressure developed during cardiac systole was either not great enough to open the aortic valves at all (pulse deficit) or was only sufficient to open the valves and to expel a small amount of blood, so that the net result so far as the propulsion of blood is concerned was a decrease. We do not know what factors were responsible for the decreased effectiveness of the beats. Among possible ones there may have been in the first place rapid rate combined with decreased ventricular filling, due to shortening of the diastolic period, and on this account decreased flow and output (8). In the second place, as we have previously shown (9), dilatation of the heart may have occurred sometimes to the extent that the muscle fibers attained a length greater than optimal so that the heart began to fail in output. In the third place, continuous rapid rates may have brought on a state of fatigue associated perhaps with a fall in aortic pressure, consequent decrease in the rate of coronary artery flow, followed by undernutrition of the muscle and decrease in contractile function. What part each of these factors played in the net result naturally cannot be estimated.

SUMMARY

The rate of blood flow and pulse deficit have been correlated in artificially induced regular and irregular tachycardia in normal unanesthetized dogs. It was found that

- 1 During rapid auricular fibrillation the rate of blood flow was decreased and a pulse deficit was present

2 During regular tachycardia there was no pulse deficit when the rate of blood flow was unchanged, but a pulse deficit was present when the rate of blood flow was decreased

3 We have shown, what we supposed was the case, namely, that there is a positive correlation between rate of blood flow and pulse deficit

CONCLUSIONS

In spite of the correlation which exists between pulse deficit and rate of blood flow in these experiments, there need be and there probably is no causal relation between them. Rather they both may occur as the result of the presence of one or more other factors such as decreased filling time, decreased aortic pressure and cardiac dilatation

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STUDIES ON THE EFFECT OF CARDIAC IRREGULARITY ON THE CIRCULATION

II THE ESTIMATION OF CARDIAC OUTPUT IN DOGS SUBJECT TO ARTIFICIAL AURICULAR FIBRILLATION

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In preceding papers (1, 2, 3) we have reported observations upon the rate of blood flow in regular and irregular tachycardias in normal unanesthetized dogs. In those experiments the values for the relative blood flow were obtained by calculating the ratio of the oxygen removed from each liter of blood by the tissues during the artificial rhythm to the oxygen removed during the normal rhythm, the ratio during the normal period being placed at 100. We did not estimate the oxygen consumption because of the reaction of untrained unanesthetized animals to the procedures used in measuring it. We did not wish to anesthetize the animals because of the secondary changes that accompany anesthesia. Because of the undesirable effect of morphine on the respiration and in slowing the heart rate we decided against its use.

We have also performed a few experiments on trained unanesthetized dogs. In these we have been able to measure the oxygen consumption and calculate the minute volume output of the heart (Fick's method). The results in these experiments agreed so closely with the calculations made of the relative blood flow that it seemed useless to accumulate a larger amount of data on the minute volume output of the heart under these conditions than is here presented.

METHODS

All the dogs were trained to breathe in a Benedict spirometer before they were used in these experiments for 20 to 30 minutes a day for 10 days to 2 weeks. At the end of this time they lay quietly on the board during metabolism tests without

emotional disturbance. It was possible to decide at the first or second trial whether a given dog was apt to be satisfactory and we continued to train only those showing evidence of being adaptable. The rubber mask described by Blalock was used and found to be satisfactory (4).

After the dogs were sufficiently trained they were operated on in order to sew wire electrodes to the right auricles as previously described (1). Twenty-four hours after this preliminary operation the heart was stimulated through these electrodes and the effect of the induced rhythm on the cardiac output studied. The dogs were in a basal metabolic state on the day of the experiment and lay quietly on the board without anesthesia. Samples of arterial blood were drawn from a femoral artery and those of mixed venous blood from the right ventricle by means of a special cannula inserted into that chamber through the right external jugular vein (5). The oxygen content of these samples was estimated by the Van Slyke and Neill manometric method (6). The difference between the oxygen content of the arterial and of the mixed venous blood gives the amount of oxygen removed from the blood by the tissues or, from the point of view of the lesser circulation, the amount of oxygen taken up by the blood in passing through the lungs. Immediately after the blood samples were drawn the oxygen consumption was measured with a Benedict spirometer equipped with a graphic recording drum.

Data were therefore at hand for calculating the minute volume output of the heart according to the principle of Fick (7)

$$\frac{\text{Cubic centimeters of oxygen consumed per minute}}{\text{Amount of oxygen absorbed by 1 cc. of blood in passing through the lungs}} = \text{Cubic centimeters of blood passing through the lungs per minute}$$

Estimations of the cardiac output were made during the normal control period and again 60 minutes after the onset of artificial fibrillation of the auricles and while this was still present. Electrocardiograms and simultaneous pulse tracings were taken at the time the cardiac output was measured in order to be certain of the rhythm then present as well as to calculate the ventricular rate and pulse deficit (3).

In 4 dogs we have measured the volume output of the heart during the normal rhythm and during auricular fibrillation. In one dog we have observations as well during regular tachycardia. As before, faradic current was used to bring on auricular fibrillation (1) and rapidly repeated single induced break shocks to institute regular tachycardia (2).

OBSERVATIONS

The effect of auricular fibrillation on the oxygen consumption. The oxygen consumption remained constant throughout these experiments. The change varied between a 2 per cent increase and an 8 per cent decrease, only one dog (dog C) showing a change of this magnitude.

TABLE I
Effect of irregular tachycardia (auricular fibrillation) on the cardiac output in dogs

Dog number	Weight kgr.	Time with reference to stimu- lation	O ₂ content		O ₂ removed from each liter of blood	Blood flow per cent of initial	Decrease in blood flow	Arterio-venous differ- ence	Oxygen consumption	Cardiac output per minute	Output per cent of initial	Decrease in output	O ₂ capacity	O ₂ saturation		Rhythm	Duration of stimulation	Heart rate (electro- cardiogram)	Femoral pulse rate	Pulse deficit	Change in oxygen con- sumption from initial
			Arterial	Mixed venous										ml	per cent			per minute	per minute	per minute	per cent
A	10.5	Before	11.27	7.98	3.29	100		7.37	82.01	112	100	23	11.63	96	1.68	2		180	180	0	+2
		During	11.38	7.04	4.34	76	24	9.72	84.0	864	77		11.63	97	8.60	5	60	330	120	210	
B	11.8	Before	9.29	5.51	3.78	100		8.47	145.41	716	100	29	9.50	96	8.75	5		160	160	0	-4
		During	9.07	3.93	5.14	73	27	11.51	140.51	220	71		9.49	94	6.40	8	60	140	130	130	
C	15.2	Before	10.74	6.28	4.46	100		9.90	113.01	131	100	22	11.47	92	8.54	4		200	200	0	-8
		During	11.38	6.13	5.25	85	15	11.76	104.0	884	78		11.75	96	1.52	2	60	340	140	200	
D	19.1	Before	10.55	7.11	3.44	100		7.71	223.02	892	100	22	10.92	95	8.64	7		200	200	0	-2
		During	10.40	6.05	4.35	79	21	9.74	220.02	258	78		10.63	97	6.56	8	60	310	140	170	

* O₂ removed from each liter of blood multiplied by 2.24

† Before calculating the oxygen saturations 0.09 mM and 0.04 mM O₂ (the amounts of oxygen in physical solution) were subtracted from the arterial and mixed venous oxygen contents respectively

‡ In this column + indicates increase and - decrease.

§ N R. = normal rhythm.

¶ A F. = auricular fibrillation

TABLE 2
The cardiac output in dog E during regular tachycardia and auricular fibrillation

Dog number	Weight	Time with reference to stimulation	O ₂ content		O ₂ removed from each liter of blood	Blood flow per cent of initial	Decrease in blood flow	Arterio venous difference*	Oxygen consumption	Cardiac output per minute	Output per cent of initial	Decrease in output	O ₂ capacity†	O ₂ saturation		Rhythm	Duration of stimulation	Heart rate (electrocardiogram)	Duration of rest after stimulation	Change in oxygen consumption from initial‡
17	17.8	Before	Arterial	mM	mM	per cent	per cent	volume per cent	cc per minute	cc	per cent	per cent	mM	per cent	per cent	N R §	min	per minute	hours	
			Mixed venous	mM	mM	per cent	per cent	per cent	cc per minute		per cent	per cent		per cent	per cent					
		During	Arterial	10 29	7 41	2 88	100	6 45	144	0 2,232	100	28	10 42	97 8	70 7	A N R ¶	60	150	1	-1
			Mixed venous	10 43	6 44	3 99	72	8 94	143	0 1,600	72		10 34	100 0	61 8					
17	17.8	Before	Arterial	10 39	6 75	3 64	79	8 15	141	0 1,730	78	22	11 03	93 4	60 8	N R	60	150	1	-2
			Mixed venous	10 50	5 68	4 82	59	10 80	145	0 1,342	60	40	11 22	92 7	50 2					
		During	Arterial	10 39	6 75	3 64	79	8 15	141	0 1,730	78	22	11 03	93 4	60 8	A F	60	360		+1
			Mixed venous	10 50	5 68	4 82	59	10 80	145	0 1,342	60	40	11 22	92 7	50 2					

* O₂ removed from each liter of blood multiplied by 2.24

† Before calculating the oxygen saturations 0.09 mM and 0.04 mM O₂ (the amounts of oxygen in physical solution) were subtracted from the arterial and mixed venous oxygen contents respectively

‡ In this column + indicates increase and - decrease

§ N R = normal rhythm

¶ A N R = artificial normal rhythm

|| A F = auricular fibrillation

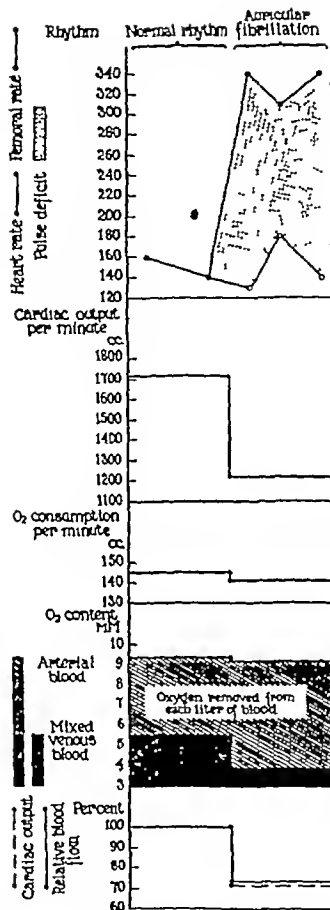


FIG 1 THE EFFECT OF AURICULAR FIBRILLATION UPON THE CARDIAC OUTPUT AND OXYGEN CONSUMPTION IN DOG B IS INDICATED GRAPHICALLY IN THIS FIGURE

The change in cardiac output is compared with the relative blood flow. During the normal rhythm they are both represented by 100 per cent and the lines coincide. During auricular fibrillation the cardiac output is decreased to 71 per cent of its initial value, while the relative blood flow fell to 73 per cent of its initial flow. The difference between these two is only 2 per cent.

(table 1) These variations are well within the limit of error involved in this method of measuring the oxygen consumption

The effect of auricular fibrillation on the cardiac output per minute
There are observations on 4 dogs. In all there was a decrease in the cardiac output per minute below the level found during the normal rhythm. The decrease varied^b between 22 and 29 per cent of the initial output (table 1). The ventricular rates during the normal rhythm ranged from 160 to 200 per minute and during auricular fibrillation between 310 and 340. During the normal rhythm a pulse deficit was not present, while during auricular fibrillation it varied between 130 and 210 per minute.

Comparison of the effect of auricular fibrillation and regular tachycardia on the cardiac output

In dog E (table 2) the cardiac output was measured during regular tachycardia as well as during auricular fibrillation. The oxygen consumption remained constant, there was a 2 per cent decrease and 1 per cent increase. The cardiac output in this dog decreased 28 per cent during regular tachycardia of 390 per minute. After a short rest period the cardiac output increased slightly toward normal. Then, when auricular fibrillation was instituted, the cardiac output decreased to 40 per cent below the initial value. This dog belongs to the small group of dogs in which the rate of blood flow was found to decrease during regular tachycardia (2).

A comparison of the changes in the relative blood flow and the cardiac output during auricular fibrillation and regular tachycardia

There is close agreement between the changes in relative blood flow and the percentage changes in the minute volume output of the heart in these experiments. In dog B the cardiac output was decreased from 1716 cc per minute during the normal rhythm to 1220 cc per minute during rapid auricular fibrillation (fig. 1), that is to say it fell to only 71 per cent of the normal output. The relative blood flow during the period of auricular fibrillation was 72 per cent of the flow during that of the normal rhythm. There was agreement, therefore, between the two measurements, the cardiac output and relative blood flow to

within 2 per cent. The decreases in the relative blood flow in these dogs ranged from 15 to 41 per cent, the decreases in cardiac output, from 22 to 40 per cent (tables 1 and 2). For any one dog the two agree within 2 per cent in all instances except one, in this one (dog C) the difference was 7 per cent. This is within the limit of error of the methods for only changes greater than 10 per cent have been considered significant.

DISCUSSION

The measurements of relative blood flow in these experiments agree with the changes in cardiac output whenever this was actually measured. The estimations of the relative blood flow were based on the assumption that the metabolism of the dogs (oxygen consumption) remained constant during the period of the experiments. We put this to test, we measured the oxygen consumption in these animals during the artificial rhythms and found that it remained constant. The assumptions made in the preceding papers (1, 2 and 3), therefore, that metabolism remained constant and that the changes which we observed were due to changes in rate of blood flow and not to changes in tissue metabolism, were therefore correct, and our inferences based on these assumptions are probably valid.

From these experiments we gain no further insight into the mechanism which is responsible for the decreased cardiac output or decreased rate of blood flow in auricular fibrillation. This subject has been discussed in another paper (3).

SUMMARY

We have measured the cardiac output of normal unanesthetized dogs during auricular fibrillation and during regular tachycardia and found that

- 1 Under the conditions of these experiments the oxygen consumption of the dogs remains constant. This is true whether the natural normal rhythm is present or whether it is that of artificial auricular fibrillation or regular tachycardia.

- 2 The cardiac output of the heart per minute is less during rapid auricular fibrillation than it is during the normal slower rhythm.

3 The estimations of the relative blood flow were found to run parallel with the changes in cardiac output measured by the method of Fick during artificial auricular fibrillation and regular tachycardia as well as during the natural normal rhythm

CONCLUSIONS

1 The heart is less effective in the propulsion of blood during rapid auricular fibrillation than it is during the normal slower rhythm

2 Since the oxygen consumption remains constant in these experiments, calculations of the relative blood flow in experiments carried out in a similar manner are valid and the conclusions at which we have previously arrived from such data are valid

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CLINICAL STUDIES ON THE VELOCITY OF BLOOD FLOW

IX. THE PULMONARY CIRCULATION TIME, THE VELOCITY OF VENOUS BLOOD FLOW TO THE HEART, AND RELATED ASPECTS OF THE CIRCULATION IN PATIENTS WITH CARDIOVASCULAR DISEASE¹

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INTRODUCTION

This paper presents the first study of the pulmonary circulation time in cardiovascular disease, and its relation to the velocity of venous blood flow in the arm, to the vital capacity of the lungs, to the arterial and venous blood pressures, and to the clinical symptoms and signs. The early occurrence of dyspnea and the early reduction of vital capacity are among the first disturbances in cardiac failure and indicate early changes in the dynamics of the circulation of blood through the lungs. The physiological and pathological importance of the pulmonary blood flow has consequently always attracted considerable interest but, until now, the peculiar inaccessibility of the pulmonary vessels has necessitated recourse to animal experimentation for direct observations. Unfortunately, however, such experiments reproduce but imperfectly and crudely conditions comparable to clinical cardiovascular disease. In man, on the other hand, only indirect observations have been possible by measurements such as the pulmonary minute volume flow according to the principle of Fick. Such observations are unsatisfactory in the presence of dyspnea and demand considerable coöperation on the part of the patient.

In preceding communications (1) (2) (3) the time of the circulation from the right antecubital vein to the left antecubital artery was

¹ This investigation was aided by a grant from the DeLamar Mobile Research Fund of Harvard University.

studied in patients with cardiovascular disease. Such an "arm to arm circulation time" is a rather complex expression of the peripheral arm blood flow as well as of the central pulmonary blood flow. By means of the technique described in preceding communications (4) (5), measurement of the time of arrival of the active deposit of radium in the right chambers of the heart has become possible. The time that elapses between the injection of the active deposit into the antecubital vein and the arrival of the active deposit in the right chambers of the heart has been termed "the arm to heart time" for it is a measure of the velocity of the venous blood of the arm to the heart. The time that elapses between the arrival of the active deposit of radium in the right chambers of the heart and its arrival in the arteries about the elbow of the arm may be called "the crude pulmonary circulation time." Although the "crude pulmonary circulation time" includes the time of transit of the active deposit from the heart to the antecubital arteries, the velocity of arterial blood flow, particularly in vessels as large as the aorta, the subclavian, and brachial arteries, is conspicuously rapid and must be relatively short compared to the actual pulmonary circulation time. For practical purposes the crude pulmonary circulation time provides an estimate of the velocity of blood flow through the lungs. Consequently it seemed desirable to study the pulmonary and the arm blood flow in cardiovascular disease and their relation to the other aspects of the circulation above cited. As in a previous communication, the patients have been grouped according to the etiology of their cardiovascular disease in order to learn whether the sequence of events in the development of cardiac failure differs according to the etiology and according to the corresponding types of lesions produced.

METHOD

The procedures employed were those described in preceding studies (4) (5) on the pulmonary circulation time in normal resting individuals. The conditions of the tests were identical except that in some patients with circulatory insufficiency slightly larger amounts of active deposit of radium (8 to 10 millicuries) were injected. In brief, venous pressure was measured directly by the venipuncture method of Montz and Tabora, the vital capacity, by means of a Collins spirometer. The

velocity of blood flow was measured by injecting small amounts of active deposit of radium into the antecubital veins of the right arm and detecting the time of arrival first, in the right chambers of the heart, and later, in the antecubital arteries about the elbow of the left arm.

As previously pointed out, the advantages of the method are as follows (1) a quantitative and objective measurement of a fundamental and hitherto unstudied aspect of the circulation is made feasible, (2) no cooperation on the part of the patient is necessary, (3) the substance injected is non toxic in the amounts utilized, (4) measurements can be repeated after three hours, (5) the velocity of the pulmonary flow can be estimated for the first time in man, (6) the variability of the peripheral capillary circulation is largely obviated, and (7), since with the arrival of the active deposit in the antebrachial arteries, the radiations from the active deposit automatically cause registration of the time of arrival, withdrawal of blood is not necessary. The method also possesses certain limitations. The "circulation time" expresses the time necessary for the transit of the fastest particle through the shortest path and does not directly measure the mean velocity. That such a "circulation time" is closely related, however, to the mean velocity, at least in normal individuals, is borne out by considerations discussed elsewhere.

The interval between the moment of injection and the time of arrival of the active deposit in the right auricle is called "the arm to heart time." The time required for the active deposit to travel from the right auricle to the antecubital arteries is termed "the crude pulmonary circulation time." By applying a standard correction of 4.3 seconds based on other measurements secured by us in the same normal individuals, the actual pulmonary circulation time was estimated (5). In 112 normal persons, the average arm to arm circulation time was 17.5 seconds. In 58 normal persons, the arm to heart time averaged 6.6 seconds, the crude pulmonary circulation time, 10.8 seconds, and the actual pulmonary circulation time, 6.5 seconds. The arm to arm circulation time of some of the patients included in this study has been utilized in preceding communications (3) (4).

I THE PULMONARY CIRCULATION TIME, THE VELOCITY OF VENOUS FLOW TO THE RIGHT AURICLE, AND THEIR RELATION TO OTHER ASPECTS OF THE CIRCULATION IN PATIENTS WITH RHEUMATIC HEART DISEASE

Rheumatic infection of the heart causes its serious effects in at least three ways (1) by invasion of the myocardium, (2) by deformation of the valves, (3) by producing conditions favorable for the occurrence of auricular fibrillation. In order to learn the relative importance of these factors in affecting the velocity of blood flow through the lungs and of the venous blood to the right auricle, patients with rheumatic heart disease (table 1) have been grouped in three classes

A Patients after acute rheumatic fever but without evidence of valvular damage

The two patients, F D (no 292) and G (no 267), represent the immediate and the very late effects of myocardial involvement uncomplicated by any demonstrable effect on the valves or on the rhythm. F D (no 292), who had recovered from acute rheumatic fever but one week previously, showed a normal pulmonary circulation time, a normal velocity of venous blood to the right auricle, a normal vital capacity, normal venous and arterial blood pressures, and a normal electrocardiographic tracing. G (no 267), on the other hand, although he showed neither evidence of valvular damage nor disturbance of rhythm, had been troubled by increasing dyspnea for four months and by orthopnea for three weeks. He showed a rapid ventricular rate, squeaking rhonchi over the bases of the lungs, and a lowered vital capacity. The pulmonary circulation time was definitely prolonged (twenty-four seconds) while the velocity of venous blood to the right auricle was within the limits of normal (seven seconds). In this instance, the rheumatic damage was confined to the myocardium while the valves, according to clinical evidence, were uninvolved.

B Patients with rheumatic valvular heart disease with regular rhythm

Of the eight patients in this group, the first seven showed pulmonary circulation times within normal limits. It should be emphasized that with the exception of patient R F (no 363), who became dyspneic only on walking up one flight of stairs, none of these seven patients

TABLE 1
The pulmonary circulation time the arm to heart time and their relation to other aspects of the circulation in patients with rheumatic heart disease

Test number	Date	Name	Age	Temperature	Pulse	Surface area square meter	Venous pressure cm H ₂ O	Arterial pressure		Vital capacity cc	Vital capacity per square meter	Circulation time				Circulation time per square meter				Injected
								Systolic mm. Hg	Diastolic mm. Hg			Arm to heart sec.	Pulmonary sec.	Arm to arm sec.	Arm to heart sec.	Pulmonary sec.	Arm to arm sec.			
Group A. Patients convalescent from acute rheumatic fever but without evidence of valvular damage																				
292	November 4 1926	F D	39	98.3	88	1.52	-2.0	138	72	3,300	2 172	5.0	9.0	14.0	3.3	5.9	9.2	4.5		
267	October 19 1926	G			142	1.67	5.0	120	54	2 000	1,197	7.0	24.0	31.0	4.1	14.4	18.5	5.2		
Group B. Patients with rheumatic valvular heart disease with regular rhythm																				
376	February 3 1927	A. C	15	99.1	108	1.52	2.5	126	66	3,350	2 205	3.5	8.0	11.5	2.3	5.2	7.5	6.0		
287	October 28 1926	K N	23	97.8	88	1.74		180	66	5 000	2 816	7.0	8.0	15.0	4.0	4.6	8.6	4.5		
338	January 6, 1927	F M	30	98.8	85	1.68	4.0	124	74			4.5	9.0	13.5	2.7	5.3	8.0	7.0		
340	January 6, 1927	J G	24	98.8	88	1.76	3.5	134	50	4 350	2,470	5.5	10.0	15.5	3.1	5.7	8.8	6.0		
363	February 10 1927	R F	22	98.6	66	1.76	9.5	142	78	3,900	2,215	16.0	11.0	27.0	9.1	6.2	15.3	8.0		
368	February 16, 1927	M E.	22	97.8	59	1.59	1.5	108	50	3 600	2,262	12.0	11.4	23.5	7.5	7.2	14.7	7.0		
283	October 28 1926	W O	42	99.2	101	1.88	-1.0	142	42	3,200	1,702	4.0	15.0	19.0	2.1	7.9	10.0	5.0		
369	February 16, 1927	P G	22	98.8	92	1.67	10.5			2,400	1,437	17.0	18.5	35.5	10.2	11.0	21.2			
Group C. Patients with rheumatic valvular heart disease with fibrillation of the auricles																				
258	September 30 1926	D S	40	98.4	64	1.60	4.0	130	85	2,300	1,438	11.0	19.0	30.0	6.8	11.8	18.6			
324	December 7, 1926	S C.	26	96.6	76	1.57	10.0	115	66	2 575	1 694	9.5	19.0	28.5	6.0	11.7	17.7	9.5		
265	October 19, 1926	S C	26	97.4	75	1.50	4.2	105	40	2,650	1,766	9.0	20.0	29.0	6.0	13.3	19.3	5.5		
406	April 6, 1927	L G	37	98.2	52	1.79	14.5			2,600	1,452	14.0	29.0	43.0	7.8	16.2	24.0	9.0		
358	February 9, 1927	H. M.	27	97.4	45	1.60	7.5	106	84	3 050	1 906	14.0	38.0	52.0	8.7	23.8	32.5	8.0		

had had symptoms or signs of circulatory insufficiency in spite of some having clinical evidence of advanced valvular lesions. Patient P G (no 369), on the other hand, showed symptoms of circulatory insufficiency at the time of test, and his pulmonary circulation time was prolonged. In the first seven patients in whom the circulation was clinically entirely compensated, the venous pressure averaged 8.3 cm of water (average normal 7.3), the vital capacity of the lungs 2278 cc per square meter of body surface (average normal 2376 cc), the arm to heart time, 7.5 seconds (average normal 6.6 seconds), and the crude pulmonary circulation time 10.4 seconds (average normal 10.8 seconds). It should be noted that the measurements on these patients coincide within the limit of error to the values found in a larger group of normal individuals.

The pulmonary circulation times found in the first seven patients demonstrate that in spite of unquestionable evidence of valvular deformity, the myocardium may be capable of maintaining a normal speed of blood flow through the lungs. The absence of previous symptoms and signs of circulatory insufficiency, the practically normal venous pressure, and the normal vital capacities of the lungs are in accord with the normal speed of blood flow.

C Patients with rheumatic valvular heart disease with fibrillation of the auricles

The venous pressure in the four patients in this group averaged 14.1 cm of water (average normal 7.3 cm), the vital capacity, 1088 cc per square meter of body surface (average normal 2376 cc), the arm to heart time, 12.5 seconds (average normal 6.6 seconds), and the crude pulmonary circulation time, 21.6 seconds (average normal 10.8 seconds).

The pulmonary circulation times of these patients were, in all cases, more prolonged than in the presence of group B with regular ventricular rhythm, and it should be noted that, likewise, all the patients with auricular fibrillation had suffered from severe circulatory decompensation and showed at the time of test symptoms or signs of congestive failure. Comparison of the measurements with the clinical summaries shows that in each patient the arm to heart time, the pulmonary circulation time, and the vital capacity of the lungs cor-

responded closely to the degree of circulatory compensation whereas the venous pressure varied considerably

Measurements 265 and 324 are of interest since they were performed on the same patient S. C. almost six weeks apart. His condition, according to clinical signs and symptoms, according to the vital capacity, and to the pulmonary circulation time, was approximately the same at the time of both tests. This is in harmony with our general experience that the velocity of blood flow parallels, in general, the degree of circulatory competence and as such provides an objective index of the degree of circulatory compensation

Discussion

The patients of groups A, B, and C show, so far as it is possible to differentiate them clinically, (1) the effects of rheumatic fever without evidence of valvular damage or disturbance in rhythm, (2) the effects of rheumatic fever with deformation of the valves, and (3) the effects of rheumatic fever on the velocity of blood flow when, in addition to the valvular deformity, fibrillation of the auricles is present

A consideration of the foregoing data emphasizes the importance of myocardial damage since the velocity of blood flow through the lungs may be seriously slowed even without clinical evidence of valvular damage. On the other hand, if the myocardium is less affected the velocity of blood flow may be normal though the mitral or aortic valves are seriously damaged

The two patients of group A typify the cardiovascular effects of rheumatic fever in the absence of valvular damage or disturbance in rhythm. The somewhat increased pulmonary blood velocity in patient F. D. (no. 292) corresponds to our findings in the arm to arm blood velocity soon after the clinical subsidence of the rheumatic infection but before evidence of valvular damage appears. As was then pointed out, (1) the somewhat increased velocity of the blood stream conforms to the other clinical evidences of cardiac hyperactivity such as forcible precordial pulsation, rapid ventricular rate, and flushed skin. Whether such patients always manifest myocardial damage later cannot be stated from our observations, although clinical experience suggests that the heart muscle may frequently escape any evident change. According to the findings in patient G. (no. 267) the myocardium

may be severely damaged without evidence of valvular deformity for, although the peripheral flow from the arm to the right auricle was within the limits of normal, the velocity of blood flow through the lungs was greatly slowed. The vital capacity was likewise reduced while the venous pressure was within normal limits.

The findings in the patients of group B indicate that generally myocardial involvement is less than that in patient G (no 267), for in seven of the eight patients studied, in spite of the additional work demanded of the myocardium because of valvular deformity, the heart muscle was able to maintain a velocity of pulmonary blood flow within the limits of normal.

The patients of group C showed fibrillation of the auricles in addition to the valvular damage, and as might have been expected, the reduction of the velocity of blood flow was in general greater. Whether this slowing is due to the disturbance in rhythm or whether such slowing simply tends to occur in the more severely damaged hearts will be discussed in a later communication.

The slowing of the blood flow through the lungs early in circulatory failure in rheumatic valvular heart disease may well be due to increased pressure in the pulmonary vessels. With insufficiency of the mitral valve and cardiac insufficiency, Straub (6) has shown that the left intra-auricular pressure rises and, in some experiments, also the pressure in the pulmonary artery and right auricle. Under such circumstances an increased amount of blood may be accommodated in the readily distensible pulmonary vessels. The resulting increase in total cross sectional diameter of the flowing stream would tend to cause a reduction in velocity if unattended by a proportionate increase in the volume flow.

The first seven patients of group B showed the signs of mitral insufficiency, and, with the exceptions of K N (no 287) and F M (no 338), the signs of mitral stenosis. With regurgitation of part of the left ventricular contents at each systole and with narrowing of the mitral orifice, the filling of the ventricle by the left auricle is hindered. According to Kornfeld (7), the total quantity of the blood in the lungs is increased and the minute volume flow and blood velocity are diminished under such circumstances. Straub (8) working with a heart-lung preparation also observed a rise in the left intra-auricular pressure.

but found no increase in the right auricular or intra-ventricular pressure. On the contrary, the maximal right ventricular pressure appeared to decrease. Similar results were obtained by Gerhardt (9), who believed that in compensated valvular lesions excess accumulation of blood is accommodated in the pulmonary veins.

The finding of normal pulmonary circulation times and arm to heart times in two patients, K. N. (no 287) and F. M. (no 338), who showed the clinical signs of mitral insufficiency and in five patients (nos 376, 340, 363, 368, 283), who showed, in addition to mitral insufficiency, the signs of mitral stenosis, favors the hypothesis of Straub and Gerhardt that in man dilatation and hypertrophy of the left auricle accommodates the regurgitated blood and forces the increased amount through the narrowed mitral orifice without slowing the time of blood

TABLE 2

Averages of findings in patients of groups B and C with rheumatic valvular disease

	Regular rhythm	Auricular fibrillation
Arm to heart time	9 seconds	12 seconds
Pulmonary circulation time (crude)	12 seconds	26 seconds
Venous pressure	9 cm. water	14 cm. water
Vital capacity per square meter	2 068 cc.	1 704 cc.

flow. Only when the auricle becomes incompetent does engorgement of the pulmonary vessels occur with retardation in the pulmonary blood flow.

The general decrease in velocity of blood flow through the lungs in patients with auricular fibrillation (table 2), is probably due to several causes. The occurrence of auricular fibrillation may well be an expression of more profound myocardial damage. Although in arteriosclerotic patients with auricular fibrillation we have noted occasionally but slight reduction in the velocity of blood flow, blood can flow far more easily from auricle to ventricle in such patients than in those whose mitral valve is stenosed. In the latter, auricular systole may assume a rôle of greater importance than it does normally. With paralysis of the auricle, however, blood flow from auricle to ventricle depends solely on the difference in pressure. Under these circumstances and especially when the mitral orifice is narrowed and the

length of diastole is curtailed by the rapid and irregular ventricular rate, adequate ventricular filling becomes difficult. The importance of the rôle of the auricle in mitral stenosis is evidenced by hypertrophy of the auricular muscle and of the right ventricle as well as by the accentuation of the pulmonic second sound.

II THE PULMONARY CIRCULATION TIME, THE VELOCITY OF VENOUS BLOOD FLOW AND RELATED ASPECTS OF THE CIRCULATION IN PATIENTS WITH SYPHILITIC HEART DISEASE

Eleven measurements of the pulmonary circulation time and related aspects of the circulation were made in eight patients. The venous pressure of all the subjects in this group averaged 10.5 cm of water (average normal, 7.3 cm), the vital capacity, 1412 cc per square meter of body surface (average normal, 2376 cc), the crude pulmonary circulation time, 19.9 seconds (average normal, 10.8 seconds), and the arm to heart time, 10.0 seconds (average normal 6.6 seconds).

Practically all the patients complained of paroxysmal dyspnea and substernal pain, and it should be noted, that although the pulmonary circulation times were within the limits of normal in patients J. P. (no 240), J. C. (nos 276, 293, 325), P. T. (no 326) and T. P. (no 318), the blood flow through the lungs was slower than the normal average in all except J. P. (no 240). The other four patients of this group all showed a more conspicuous slowing of the blood flow through the lungs and it should be observed that all had recently suffered congestive failure, or, at the time of test, showed definite physical signs of circulatory insufficiency. M. B. (no 316), for example, complained of dyspnea on the slightest exertion, while patients A. S. (no 271) and A. J. (no 330) showed physical signs of passive congestion. The crude pulmonary circulation times of twenty-six and thirty-three seconds parallel the other clinical evidences of circulatory insufficiency. The findings in patient W. H. are of interest for the pulmonary circulation time was measured on two occasions when, according to physical examination, his condition was unchanged. At the time of the second test, September 22, 1926, he stated that he felt distinctly better than at the time of the first test, and his pulmonary circulation time was

TABLE 3
The pulmonary circulation time, the arm to heart time and their relation to other aspects of the circulation in patients with syphilitic heart disease

Test number	Date	Tab	Age	Temperature	Pulse	Surface area square meters	Venous pressure mm Hg	Arterial pressure		Vital capacity		Circulation time						Circulation time per square meter		Infected
								Systolic	Diastolic	cc	cc	Arm to heart	Pulmonary	Arm to arm	Arm to heart	Pulmonary	Arm to arm	Arm to heart	Pulmonary	
240	September 2, 1928	J P			84	1.72	7.5	140	75	2,500	1,453	7.0	10.0	17.0	4.0	5.8	9.8	10.0	10.0	
276	October 26	J C	52	98.8	70	1.92		136	0	2,700	1,406	8.0	14.0	22.0	4.1	7.2	11.3	5.0	5.0	
293	November 4	J C	52	98.2	82	1.92		162	0	2,750	1,434	4.0	16.0	20.0	2.1	8.3	10.4	4.0	4.0	
326	December 7	P T	64	98.8	74	1.58	2.5	162	64	2,400	1,519	7.5	16.0	23.5	4.7	10.1	14.8	6.0	6.0	
318	November 23	T P	46	99.4	84	1.59	3.5			2,500	1,572	6.0	17.0	23.0	3.7	10.7	14.4	5.0	5.0	
325	December 7	J C	52	98.7	72	1.92	1.5			1,925	1,005	8.0	18.0	26.0	4.2	9.4	13.6			
316	November 23	M B	55	98.0	98	1.77	9.5	172	0			5.5	19.5	25.0	3.1	11.0	14.1	9.0	9.0	
243	November 22	W H	54	98.0	88	1.62	-4.0	110	40	3,000	1,852	14.0	22.0	36.0	8.6	13.5	22.1	5.4	5.4	
271	October 21	A. S.	57	95.0	89	1.58	5.0			2,300	1,455	6.0	26.0	32.0	3.7	16.4	20.1	5.0	5.0	
239	September 2	W H.	54		88	1.66						16.0	27.0	43.0	9.6	16.2	25.8			
330	December 14	A J	56	95.8	86	1.78	15.5	165	65	1,800	1,011	30.0	33.0	63.0	16.8	18.5	35.3	8.5	8.5	

twenty-two seconds, that is to say, five seconds shorter. Tests were performed on three different occasions on patient J C (no 276, 293, 325). At no time did he show clinical signs of passive congestion although he stated that he felt somewhat more dyspneic at the time of the third test, when his crude pulmonary time was eighteen seconds (four seconds longer than the first) and his vital capacity was 1005 cc per square meter of body surface against 1406 cc and 1434 cc at the earlier tests.

Discussion

The decrease in the velocity of blood flow through the lungs in patients suffering from syphilitic heart disease parallels the clinical evidences of circulatory failure but the slowing of the blood stream may not be as great as that observed in patients with rheumatic heart disease and an apparently similar degree of cardiac failure. The vital capacity in practically all subjects was considerably reduced, averaging 1378 cc per square meter of body surface. Whether this reduction in vital capacity is due to engorgement or whether it is due in part to reflex spasm, such as in bronchial asthma, cannot be stated from the available data.

The venous pressure averaged 9.9 cm of water in the six of the eight patients measured. Although this average is higher than the normal of 7.3 cm, such a small difference is probably not of any significance because of the much greater variability of the venous pressure as compared to the other measurements.

It is worthy of note that even with slowing of the blood flow through the lungs and with reduction in the vital capacity, the peripheral venous blood flow may be well within the limits of normal according to the measurement of the venous pressure and the velocity of the venous blood from the right antecubital vein to the right auricle. Excepting W H (no 243, 239) who had suffered congestive failure shortly previous to his tests, and patient A J, who had slight pitting edema on the day of the test, the arm to heart times averaged 6.5 seconds (average normal, 6.6 seconds), while the crude pulmonary circulation times averaged 17.0 seconds (average normal, 10.8 seconds). The absence of peripheral edema associated with normal arm to heart times suggests that the difference between so-called "dry heart failure" and "congestive heart failure" may be due to differences in the velocity of the

peripheral blood stream. This relation between the arm to heart time and the appearance of peripheral edema is not clear in every instance nor is a close correspondence to be expected since the arm to heart time is an index of the speed of the venous blood flow of the arm while the signs of peripheral edema characteristically appear elsewhere.

The occurrence of normal arm to heart times in aortic insufficiency is likewise evidence of the relatively late appearance of failure of the right chambers of the heart in this form of valvular defect. It is of interest to observe (table 1) that although the pulmonary circulation time in patients with syphilitic heart disease and regular rhythm averaged five seconds more (17.0 seconds) than that of patients with rheumatic heart disease and regular rhythm, the arm to heart time averaged two seconds less. This average relative shortening of seven seconds in the arm to heart time is in harmony with general clinical experience. The left auricle and ventricle labor under a great handicap in aortic insufficiency and seem to give way sooner than the right chambers, which in the earlier stages, are still capable of receiving all the venous blood from the periphery and transferring it into the pulmonary vessels. This situation contrasts with the early strain of the right ventricle in mitral stenosis and insufficiency. Consequently peripheral stasis may occur in patients with mitral stenosis while the left ventricle is still functionally capable, whereas in patients with aortic insufficiency, peripheral stasis is a sign of failure of all the chambers of the heart. It is hardly surprising that when in syphilis the right chambers of the heart fail and peripheral edema appears, the slowing of the venous blood from the arm to the heart may be fully as great as that observed in patients with rheumatic valvular disease (patients W. H. (nos. 239, 243), A. J. (no. 330)). This consideration of events explains why pulmonary congestion and peripheral stasis occur so late in aortic insufficiency and why their occurrence is of such grave prognostic import.

III THE PULMONARY CIRCULATION TIME, THE VELOCITY OF VENOUS BLOOD AND THEIR RELATION TO OTHER ASPECTS OF THE CIRCULATION IN PATIENTS WITH ARTERIOSCLEROSIS AND MYOCARDIAL DEGENERATION

The pulmonary circulation time, the velocity of venous blood from the antecubital vein to the right auricle, the venous and arterial pres-

TABLE 4

The pulmonary circulation time, the arm to heart time, and their relation to other aspects of the circulation in patients who, with evidence of arteriosclerosis and myocardial degeneration, showed regular rhythm

Test number	Date	Name	Age	Temperature	Pulse	Surface area square meters	Venous pressure cm H ₂ O	Arterial pressure		Vital capacity cc	Vital capacity per square meter	Circulation time			Circulation time per square meter			Injected multi- curies
								Systolic	Diastolic			Arm to heart	Pulmonary	Arm to arm	Arm to heart	Pulmonary	Arm to arm	
371	February 16, 1927	J C	58	99.2	84	1.87	4.0	142	90	3,800	2,021	5.5	10.0	15.5	2.9	5.4	8.3	6.5
332	December 14, 1926	N B	68	98.5	92	1.57	5.5	162	86	3,300	2,090	4.5	13.0	17.5	2.9	8.3	11.1	5.0
361	February 9, 1927	A F	60	98.2	72	1.68	-3.5	130	85	3,650	2,171	13.0	14.0	27.0	7.7	8.3	16.0	7.0
370	February 16, 1927	H S	65	98.6	74	1.32	4.0	130	70	2,100	1,591	4.0	14.5	18.5	3.0	11.0	14.0	8.0
372	February 16, 1927	J H	70	97.6	43	1.67	7.5	140	70	3,150	1,886	15.0	17.0	32.0	8.9	10.1	19.0	9.0
319	November 23, 1926	N B	68	97.8	82	1.57	6.0	176	82	3,000	1,910	5.0	18.0	23.0	3.2	11.5	14.7	
290	October 28, 1926	W L	60	99.0	74	1.57	6.0	176	82	3,000	1,910	6.0	19.0	25.0				
389	March 14, 1927	J H	70	97.4	38	1.57	2.0	122	68	3,100	1,856	11.0	21.0	32.0	6.6	12.6	19.2	8.0
242	September 22, 1926	J B	57	96.6	64	1.77	-7.0	118	80	3,750	2,118	14.0	25.0	39.0	7.9	14.1	22.0	4.6
295	November 4, 1926	M	72	98.4	62	1.46	3.5	114	50	3,900	2,038	12.0	27.0	39.0	8.2	18.5	26.7	
241	September 22, 1926	D M	78	95.2	72	1.57	1.5	114	50	3,900	2,038	13.0	32.0	45.0	8.3	20.3	28.6	4.8
284	October 28, 1926	J G	60	97.2	100	1.57	3.5	125	90	2,000	1,273	18.0	33.0	51.0	11.4	21.0	32.4	4.5
360	February 9, 1927	M H	48	97.2	77	1.78	17.0	138	116	1,800	1,011	25.5	42.0	67.5	14.3	23.6	37.9	9.0
341	January 6, 1927	T R	47	96.8	82	1.91	17.5	138	110	1,000	523	22.5	45.5	68.0	11.8	23.8	35.6	8.0
312	November 19, 1926	J G	60	96.5	80	1.57	15.0	152	112	1,000	637	31.0	67.0	98.0	19.7	42.7	62.4	7.9

tures, the vital capacity of the lungs, and the clinical signs and symptoms were studied in sixteen patients with generalized arteriosclerosis and with myocardial degeneration (tables 4 and 8). The venous pressure averaged 10.0 cm of water (average normal, 7.3 cm), the vital capacity 1506 cc. per square meter of body surface (average normal, 2376 cc.), the arm to heart time, 13.0 seconds (average normal, 6.6 seconds), and the crude pulmonary circulation time, 26 seconds (average normal, 10.8 seconds). In two patients the circulatory tests were repeated on three different occasions, and in two patients, on two different occasions. The subjects are divided into

TABLE 5
Patients with signs of arteriosclerosis without history of cardiac failure and without signs of congestive failure

Test number	Vital capacity	Vital capacity per square meter	Pulmonary circulation time (crude)	Arm to heart time	Venous pressure
	cc	cc	seconds	seconds	cm. H ₂ O
371	3,800	2,021	10.0	5.5	4.0
332	3,300	2,090	13.0	4.5	5.5
370	2,100	1,591	14.5	4.0	4.0
319	3,000	1,910	18.0	5.0	6.0
242	3,750	2,118	25.0	14.0	-7.0
Average	3,190	1,946	16.1	6.6	2.4

two groups, one, showing regular ventricular rhythm, the other, totally irregular rhythm.

A Patients with regular ventricular rhythm (table 4)

As has been pointed out in a previous communication, the study of patients who show circulatory insufficiency in the absence of valvular damage and arrhythmia provides an excellent opportunity to observe the practically uncomplicated effect on the circulation of but one factor, myocardial weakness. Circulatory tests were made on fifteen patients who showed regular ventricular rhythm. In two, the measurements were repeated once (table 4). These patients fall into three groups.

Group 1 (table 5) Of five tests on patients with arteriosclerosis,

but without history of cardiac failure in whom the circulation was compensated on physical examination, two of the tests (nos 332 and 319), were on the same individual, several weeks apart. In general, this group showed a vital capacity 15 per cent less, and a crude pulmonary circulation time 49 per cent greater than the average normal value found by us in normal individuals, while the venous pressure and arm to heart time were normal.

TABLE 6

Patients complaining of dyspnea on exertion but having no signs of congestive failure on physical examination at time of test

Test number	Vital capacity	Vital capacity per square meter	Pulmonary circulation time (crude)	Arm to heart time	Venous pressure
	cc	cc	seconds	seconds	cm H ₂ O
361	3,650	2,171	14 0	13 0	-3 5
272	3,150	1,886	17 0	15 0	7 5
389	3,100	1,856	21 0	11 0	2 0
295	1,550	1,062	27 0	12 0	3 5
241	3,900	2,038	32 0	13 0	1 5
Average	3,070	1,803	22 2	12 2	2 2

TABLE 7

Patients who showed at time of test signs of congestive failure

Test number	Vital capacity	Vital capacity per square meter	Pulmonary circulation time (crude)	Arm to heart time	Venous pressure
	cc	cc	seconds	seconds	cm. H ₂ O
284	2,000	1,273	33 0	18 0	3 5
360	1,800	1,011	42 0	25 5	17 0
341	1,000	523	45 0	22 5	17 5
312	1,000	637	67 0	31 0	15 0
Average	1,450	861	46 7	24 2	13 2

Group 2 (table 6) This group showed no signs of decompensation at the time of test but had previously experienced symptoms of circulatory insufficiency. The vital capacity was 24 per cent less than the normal, the crude pulmonary circulation time was 105 per cent, and the arm to heart time 84 per cent greater than the normal, while the venous pressure coincided with the normal average.

Group 3 (table 7) The group with signs of congestive failure at the time of the test had a vital capacity 36 per cent of the normal, while the crude pulmonary circulation time and the arm to heart time indicated a slowing of the blood flow to approximately one-fourth normal speed. The subjects of these tests were of advanced years and so the low vital capacity measurements may reflect the presence of pulmonary emphysema as well as of circulatory failure.

In all patients with arteriosclerosis, pulmonary circulation and vital capacity measurements showed departures from normal values that generally paralleled the clinical symptoms and signs, although this relation did not necessarily hold in each instance. In test 241, for example, the vital capacity was 2036 cc. per square meter of body surface, while the pulmonary crude circulation time was 32.0 seconds.

The relation between the appearance of edema and the slowing of the peripheral blood stream indicated by the arm to heart time is interesting. The patients of group 2 without edema had an arm to heart time of fifteen seconds or less, while the patients of group 3 with edema showed arm to heart times of eighteen seconds or more. This suggests, as has been stated, that the appearance of edema is associated with slowing of the peripheral blood stream and that the difference between so-called "dry" and "congestive" heart failure may be due to differences in the speed of the peripheral blood flow. The moderately prolonged times found in group 2, associated with dyspnea but without physical signs of congestive failure, may denote a greater collection of blood in, and dilatation of, the pulmonary vessels, just as occurs in the peripheral veins before the pressure begins to rise. The normal venous pressure associated with abnormally slow velocity of venous blood flow and the decrease in the vital capacity conform to this possibility. The appearance of edema probably does not coincide with a definite degree of slowing of the blood stream for it is also dependent on physico-chemical changes which themselves are secondary to diminished blood flow and which are influenced by many other factors.

B Patients with fibrillation of the auricles (table 8)

Of the patients who, in addition to signs of generalized arteriosclerosis and myocardial degeneration, showed complete ventricular arrhythmia, all had previously suffered congestive failure or showed such signs

TABLE 8

The pulmonary circulation time, the arm to heart time, and their relation to other aspects of the circulation in patients who with evidence of arterio-sclerosis and myocardial degeneration, showed fibrillation of the auricles

Test number	Date	Name	Age	Temperature	Pulse	Surface area square meters	Venous pressure cm H ₂ O	Arterial pressure		Vital capacity cc	Vital capacity per square meter	Circulation time				Circulation time per square meter		Injected
								Systolic mm Hg	Diastolic mm Hg			Arm to heart sec onds	Pulmonary sec onds	Arm to arm sec onds	Arm to heart sec onds	Pulmonary sec onds	Arm to arm sec onds	
362	February 9, 1927	C	66	98.6	77	1.94	5.0	132	88			5 0 15	5 20 5	2 6 7	9 10 5	8 0		
411	April 20, 1927	M M	49	97.2	53	1.92	3.5	144	82	4,200	2,189	11 0 16	0 27 0	5 7 8	3 14 0	8 0		
261	September 30, 1926	W D	55	97.4	74	1.65	10.0					15 0 27	0 42 0	9 1 16	3 25 4			
246	September 24, 1926	W D	55	98.0	42	1.65	3.0	94	65	2,100	1,272	21 0 34	0 55 0	12 7 20	6 33 3	7 8		
247	September 24, 1926	F B	65	97.6	64	1.60	-3.0	126-114	64-60	1,100	687	7 0 35	0 42 0	4 3 21	8 26 1	3 4		

at the time of test. The average vital capacity was 2230 cc. which when reduced to cubic centimeters per square meter of body surface was 1580 cc. (average normal, 2376 cc.) The average crude pulmonary circulation time was 25.6 seconds (average normal, 10.8), the average arm to heart time was 12.1 seconds (average normal, 6.6), the average venous pressure 9.0 cm. (average normal, 7.3 cm.) These four patients did not show as severe circulatory insufficiency as those patients with regular rhythm that we happened to study. This general finding as well as the results of test numbers 362 and 411 demonstrate that the velocity of blood flow may be maintained at a speed within the upper limits of normal in spite of the abnormal mechanism of auricular fibrillation.

IV. THE PULMONARY CIRCULATION TIME, THE VELOCITY OF VENOUS BLOOD TO THE HEART, AND RELATED ASPECTS OF THE CIRCULATION IN PATIENTS WITH ARTERIAL HYPERTENSION

In these patients (table 9), the venous pressure averaged 14 cm. of water or 92 per cent greater than the normal average, the vital capacity 1784 cc. per square meter of body surface or 25 per cent less than the normal, the arm to heart time 9.7 seconds or 47 per cent greater than the normal, and the crude pulmonary circulation time 15.3 seconds or 42 per cent greater than the normal. The patients have been divided into three groups.

Group A These patients exhibited no evidence of circulatory failure. The velocity of blood flow through the lungs was within the limits of normal although the general average, 12.0 seconds, was slightly higher than that shown by a larger series of normal individuals (10.8 seconds). It may not be without significance that patient T. L. who showed the most rapid velocity of blood flow was likewise the person whose blood pressure was the lowest.

Group B The distinct retardation in pulmonary blood velocity shown by patients in this group in the absence of signs or symptoms of circulatory insufficiency at rest or on exertion, as well as the tendency toward slowing in the subjects in group A, may be related to back pressure effects of arterial hypertension on the pressure within the pulmonary vessels. There is experimental evidence for this idea. Cloetta and Staubli (11) found that compression of the thoracic aorta always

TABLE 9
The pulmonary circulation time, the arm to heart time and their relation to other aspects of the circulation in patients with arterial hypertension

Test number	Date	Name	Age	Temperature	Pulse	Surface area	Venous pressure	Arterial pressure		Vital capacity	Vital capacity per square meter	Circulation time				Circulation time per square meter	Injected	
								Systolic	Diastolic			Arm to heart	Pulmonary	Arm to arm	Pulmonary			Arm to heart
Group A. Patients with compensated circulation at time of test, in whom the pulmonary circulation time was within normal limits																		
377	February 23, 1927	T L	47	97 0	76	1 81	5 0	155	100	4,000	2,210	7 0	7 5	14 5	3 9	4 1	8 0	7 0
272	October 21, 1926	E M	46	98 2	82	1 81	8 0	184	110	3,800	2,099	11 0	11 0	22 0	6 0	6 0	12 0	5 0
307	November 6, 1926	B N	57	98 1	80	1 77	10 5	180	102	3,500	1,980	3 0	12 0	15 0	1 7	6 7	8 4	4 5
331	December 14, 1926	F S	41	98 4	82	1 78	7 0	200	110	3,700	2,021	6 0	12 0	18 0	3 4	6 7	10 1	5 0
357	February 9, 1927	G M	52	98 0	60	1 78	5 5	248	128	3,400	1,910	6 0	12 0	18 0	3 4	6 7	10 1	8 0
336	January 6, 1927	A O	68	98 6	78	1 81	7 0	210	115	3,250	1,785	10 0	13 0	23 0	5 5	7 2	12 7	6 0
309	November 6, 1926	J M		98 6	58	1 79	8 5	205	104	3,650	2,039	12 0	14 0	26 0	6 7	7 9	14 6	4 0
305	November 6, 1926	H M	70	98 1	90	1 74	20 0	194	104	2,700	1,552	4 0	14 5	18 5	2 3	8 3	10 6	7 0
Group B. Patients with compensated circulation in whom the pulmonary circulation time was prolonged																		
300	November 5, 1926	M P	50	99 2	92	1 60	12 5	180	95	4,000	2,500	15 0	18 0	33 0	9 4	11 2	20 6	4 0
308	November 6, 1926	M C	57	97 2	66	1 86	8 5	192	116	4,400	2,368	12 0	19 0	31 0	6 4	10 2	16 6	4 0
304	November 6, 1926	M S	61	98 2	76	1 76	6 5	190	112	2,900	1,648	7 0	23 0	30 0	4 0	12 2	16 2	
296	November 4, 1926	M P	50	98 4	94	1 60	13 5	214	110	4,100	2,560	6 0	23 5	29 5	3 7	14 7	18 4	6 5
Group C. Patients with decompensated circulation in whom the velocity of blood flow was prolonged																		
429	May 21, 1927	C B	41	98 4	82	1 73	6 5	200	140	1,200	694	6 5	16 0	22 5	3 7	9 3	13 0	9 5
423	May 12, 1927	P F	63	98 8	81	1 96	4 5	210	120	3,500	1,786	8 0	21 0	29 0	4 1	10 7	14 8	7 0
427	May 18, 1927	C B	41	98 6	116	1 82	21 0	195	160			22 0	22 0	44 0	12 0	12 0	24 0	9 0

caused an increased lung volume, and Straub (8) and also Gerhardt, (9), likewise observed that increased arterial pressure in the greater circulation produced an increase in the volume of the lesser circulation. Such an increase in the amount of blood in the lungs would lead to increased cross sectional diameter of the stream of blood flowing through the lungs. Slowing in blood flow with prolongation of the pulmonary circulation time must then occur since the velocity of flow is inversely proportional to the cross sectional diameter of a stream. Observations by Wearn, Barr and German (12) are in accord with this hypothesis, for they observed in animals that slight compression of the abdominal aorta caused considerable dilatation of alveolar capillaries. With such an increase in the amount of blood in the lungs a decrease in the vital capacity might also be expected because of diminished lung elasticity. Although the vital capacities of the patients in groups A and B averaged 2055 cc per square meter or 86 per cent of the normal, interpretation is ambiguous because of the advanced years of most of the patients.

We emphasize these findings because they constitute the only instance in which the circulation was functionally competent in the presence of retardation in the pulmonary blood flow velocity and because the mechanism by which this slowing is produced is of considerable physiological interest.

As in the preceding study of the arm to arm velocity of blood flow, we have found that the velocity of blood flow was never greater than the normal. This indicates that increased blood pressure, which in itself would tend to increase the speed of flow, is opposed by such factors as increased peripheral resistance. If cardiac hyperactivity were primary, one would expect to find a stage in which the peripheral resistance had not as yet increased and in which the blood flow was abnormally rapid.

Group C consists of patients in whom the slowing of the blood flow was associated with the symptoms or signs of circulatory failure. This finding is in accord with our experience with other patients suffering from circulatory failure with a normal blood pressure. The degree of slowing in blood flow was approximately that observed in patients with cardiovascular failure of other etiology.

The venous pressures of patients with hypertension showed extreme variability with no evident relationship to the degree of passive con-

gestion In some patients such as B N (no 307), H M (no 305), M P (nos 296, 300), the elevation of the venous pressure was of a degree usually associated with chronic passive congestion, whereas these patients were free from such signs or symptoms There was no relation between the venous blood velocity and the venous pressure In H M (no 305), for example, the venous pressure was equivalent to 25 cm of water, the arm to heart time was 4 seconds, whereas in M P (no 300) the venous pressure was equivalent to 17.5 cm of water while the arm to heart time was 15 seconds These variations in venous pressure, unrelated as they are to changes in the velocity of blood flow, may be an expression of the vasomotor instability and hyperirritability recognized by clinicians That an increased venous pressure may be associated with arterial hypertension in the absence of circulatory failure has been observed by others (13) (14) (15)

It may be thought that because of vasomotor instability patients in group A might at times show the more prolonged circulation times of those in group B It is of interest that M P, in whom the velocity of blood flow was measured twice, showed on both occasions prolonged circulation times

SUMMARY AND CONCLUSIONS

1 Sixty-three measurements of the pulmonary circulation time, of the arm to heart time, of the venous and arterial blood pressures, and of the vital capacity of the lungs have been made in fifty-four male patients with cardiovascular disease (rheumatic, syphilitic, arteriosclerotic, arterial hypertension) and their relation to the clinical findings have been studied

2 The clinical and physiological significance of these observations is discussed

3 The methods as described in a preceding communication have been found adequate for the study of the clinical aspects of cardiovascular disease

I PATIENTS WITH RHEUMATIC HEART DISEASE

A Without valvular damage

1 Measurements were made on two patients, who showed the immediate and the very late effects of myocardial involvement subsequent to acute rheumatic fever

2 In one patient, a young adult, the symptoms and signs of severe rheumatic myocardial damage were associated with moderate slowing of the pulmonary blood flow while the peripheral blood flow from the arm to the heart was within normal limits

3 The other patient showed a slightly increased velocity of blood flow with clinical evidences of exaggerated cardiac activity following acute rheumatic fever

B With valvular damage and regular rhythm

1 Normal speed of blood flow through the lungs and from the arm to the heart demonstrates that in spite of valvular deformation, the myocardium may be capable of maintaining a normal velocity of blood flow

2 In the one patient who was dyspneic at the time of test, but who showed no signs of congestive failure, the pulmonary blood flow was slightly slower than the normal

3 These observations indicate that the slowing of blood flow in rheumatic heart disease reflects the dysfunction due to myocardial damage.

4 There is no close relationship between the degree of valvular involvement and the degree of circulatory competence as reflected by the velocity of blood flow

C With valvular damage and fibrillation of the auricles

1 The velocity of pulmonary blood flow was slowed and bore a definite relationship to the degree of circulatory insufficiency. The peripheral blood flow, as judged by the arm to heart time, while in general retarded, was not so closely related to the clinical findings

II. PATIENTS WITH SYPHILITIC HEART DISEASE

1 The decrease in the velocity of blood flow through the lungs paralleled the clinical evidences of circulatory failure except that paroxysmal dyspnea and precordial pain did not seem to be associated with quite as much slowing of the blood stream as that observed in patients with rheumatic heart disease. This suggests that paroxysmal breathlessness and pain in patients with syphilitic aortitis may be due in part to a reflex mechanism

2 Even with slowing of the blood flow through the lungs and with reduction in the vital capacity of the lungs, the peripheral blood flow was found within the limits of normal according to the measurement of the venous pressure and of the arm to heart time. This is in harmony with the late appearance of edema in aortic insufficiency.

3 Our findings suggest that the differences between so-called dry heart failure and congestive heart failure may well be due to differences in the velocity of the peripheral blood stream.

III PATIENTS WITH ARTERIOSCLEROSIS AND WITH EVIDENCES OF MYOCARDIAL DEGENERATION

A With regular rhythm

1 Of the patients in this group in whom the arm to heart time was fifteen seconds or less, none showed evidence of peripheral edema, while all patients who showed arm to heart times above this, showed signs of peripheral edema.

2 The velocity of blood flow through the lungs paralleled in general the degree of circulatory incompetence and as such provided an objective and quantitative index of the circulation.

B With fibrillation of the auricles

In two patients the velocity of blood flow through the lungs was within the upper limits of normal in spite of the abnormal mechanism of auricular fibrillation, whereas the velocity of pulmonary blood flow was moderately or greatly reduced in the two others according to the degree of circulatory failure.

IV PATIENTS WITH ARTERIAL HYPERTENSION

1 Patients with arterial hypertension who show no evidence of circulatory disability may be divided into two groups: in one, the pulmonary velocity of blood flow is within the limits of normal, whereas in the other it is retarded.

2 The arm to heart times in these subjects bore no constant relation to the pulmonary circulation time.

3 In no patients with hypertension was an abnormally rapid velocity of blood flow observed. This suggests that the fundamental

disturbance in arterial hypertension is increased peripheral resistance rather than cardiac hyperactivity

4 As in a previous study, we observed in some patients an abnormally high venous pressure in the absence of congestive failure

5 Patients with arterial hypertension and with congestive failure show a retardation in the pulmonary and peripheral blood flow similar to that in patients with a corresponding degree of circulatory failure but with a normal rhythm.

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ABSTRACTS OF HISTORIES AND PHYSICAL EXAMINATIONS

I PATIENTS WITH RHEUMATIC HEART DISEASE

292 F D Two months previously there had been swelling of the right wrist, spontaneously subsiding He had had a similar attack seven years previously One week previous to entry red, tender, swelling of right wrist and right elbow appeared Physical Examination was entirely negative at time of test The diagnosis was acute rheumatic fever

267 G had had numerous attacks of tonsilitis in the past but not rheumatic fever Ten months previously he noticed gradually increasing dyspnea and finally orthopnea, forcing him to enter the hospital Physical examination at that time showed cyanosis, orthopnea, a moderately enlarged heart with a soft systolic but no diastolic murmur The ventricular rate was about forty and electrocardiographic tracings showed the presence of partial heart block The consensus of opinion was that the patient was suffering from rheumatic myocarditis He improved and left the hospital but returned because of recurrence of the previous orthopnea Physical examination showed the apex impulse in the fifth interspace with the left border of dullness 12 cm from the midsternal line The rhythm was regular, the lungs were clear and the liver was not palpable Squeaking rhonchi were heard over both chests posteriorly There was no edema of the ankles The diagnosis was rheumatic myocarditis

376 A C entered the hospital for tonsillectomy He had had an attack of acute rheumatic fever one year previously but had never suffered from circulatory insufficiency Physical examination was normal save for a slightly enlarged heart with a systolic and rough presystolic murmur over the mitral area The diagnosis was rheumatic heart disease, mitral stenosis and insufficiency

287 K N entered the hospital because of pain and swelling of both knees

During the previous five weeks he had had acute rheumatic fever which responded to treatment by salicylates. At time of test there were no joint signs or symptoms. Physical examination. Heart. Left border of dullness 11.5 cm from midsternal line in fifth space. First sound was accentuated. Soft systolic murmur at the apex was transmitted to the axilla. There was no diastolic murmur. The diagnosis was rheumatic heart disease and mitral insufficiency.

338 F MacD. No reliable history was obtainable. There was a loud booming first sound over the apex followed by a rough systolic murmur transmitted to axilla. The heart was slightly enlarged. There were no signs of congestive failure. The diagnosis was rheumatic heart disease and mitral insufficiency.

340 J G. entered the hospital complaining of weakness and palpitation three months in duration. He had had acute rheumatic fever in childhood but had never experienced shortness of breath on exertion or other signs or symptoms of congestive circulatory failure. Physical examination was negative save for slight cardiac enlargement and the signs of mitral stenosis and insufficiency. The diagnosis was mitral stenosis and insufficiency.

363 R F. entered the hospital complaining of painful joints. He had had several attacks of acute rheumatic fever but had never experienced dyspnea except on walking up one flight of stairs. Physical examination was negative save for a moderately enlarged heart, accentuation of the second pulmonic sound, a loud blowing systolic and a rough presystolic murmur over the mitral area and a loud first sound. There was no past or present evidence of congestive failure. The diagnosis was mitral stenosis and insufficiency.

368 M E. entered the hospital complaining of painful swollen joints, fever and palpitation. He had never experienced symptoms of circulatory decompensation. At time of test, fourteen days later the heart was found slightly enlarged and a distinct diastolic and systolic murmur was heard over the apex. The joints were normal. There were no signs of circulatory insufficiency. The diagnosis was acute rheumatic fever, mitral stenosis and insufficiency.

283 W O. had had rheumatic fever 28 years and 18 years previously. At time of insurance examination 18 years previously he was told he had aortic valvular disease. He never experienced any symptoms referable to the circulatory system and entered the hospital because of acute alcoholic intoxication. He was able to lead a vigorous, normal life. Physical examination showed a well developed man with conspicuous arterial pulsations in neck vessels. Heart was moderately enlarged with the apex 14 cm to the left of the midsternal line in the fifth space. Apex impulse was heaving. There were no thrills. At apex first sound was rough and loud, second sound accentuated. Short, rough presystolic murmur and soft systolic and diastolic murmur were heard. Loud, long diastolic murmur heard along the left border of sternum and faint diastolic murmur, over the aortic area. Corrigan pulse and Duroziez's sign were present. The diagnosis was mitral stenosis and regurgitation and aortic regurgitation.

369 P G. entered hospital complaining of substernal pain. He had had rheumatic heart disease for eighteen years. Day before entry a to and fro friction

rub had been heard to left of sternum. He had occasionally experienced shortness of breath on exertion but never noted swelling of legs. Physical examination showed the heart moderately enlarged, the rhythm regular, and the physical signs of mitral stenosis and insufficiency. There were no signs of congestive circulatory failure. The diagnosis was probable acute pericarditis, mitral stenosis and insufficiency.

258 D S had had shortness of breath, attacks of sharp lancinating, non-radiating pain over the heart for several years, which followed exertion, and which lasted a minute or two. He recently had experienced marked orthopnea. One week before entry he coughed up blood-streaked sputum. Physical examination showed left border of cardiac dulness 12 cm. The apex impulse was felt in the 5th and 6th interspaces. The cardiac rhythm was totally irregular. Double murmurs were present over the apex and over the aortic area. Râles were heard over the lungs. There was edema of both ankles. Hemoglobin was 75 per cent. The diagnosis was auricular fibrillation, mitral stenosis and insufficiency.

324, 265 S C complained of shortness of breath. He had had rheumatic fever in childhood but had been well until 9 years previously, when, after pneumonia, he developed moderate shortness of breath for 8 months. During the 10 months before entry he experienced slight precordial pain on exertion with shortness of breath and palpitation, which gradually increased in severity forcing him to enter the hospital. Three days before admission, pitting edema was observed over lower legs. After admission to the hospital, on rest in bed and digitalis, he showed moderate improvement. At time of test, 265, he was still slightly orthopneic. Physical examination showed blowing systolic and diastolic murmurs over aortic and mitral areas. The liver was not palpable. There was no edema of the legs. A few moist râles were heard over the left base. Following rest in the hospital patient returned home but was compelled to re-enter hospital because of exacerbation of symptoms. At time of test no 324 patient felt well and was up and about the ward. There was no dyspnea or orthopnea. Physical examination showed no râles over chest and no edema. The liver was not palpable, and the heart was as noted above. The diagnosis was rheumatic pericarditis, auricular fibrillation, aortic stenosis and insufficiency, mitral stenosis and insufficiency.

406 E G entered hospital two weeks previous to test severely decompensated, but on rest in bed and digitalis he improved so that he was but slightly dyspneic at time of test, and was troubled only by a slight cough. Physical examination showed moderately enlarged heart, with the signs of mitral stenosis and insufficiency, total irregularity of the rhythm, signs of fluid over the base of the right lung and slight but definite pitting edema over the ankles. The diagnosis was mitral stenosis and insufficiency and auricular fibrillation.

358 H M entered hospital complaining of shortness of breath on the slightest exertion, six weeks in duration. He had no history of rheumatic fever but had had frequent sore throats. He noticed irregularity of heart action two years previously.

which had since persisted. Dyspnea had appeared three months previously and had gradually become worse. Physical examination showed moderate cardiac enlargement and the signs of mitral stenosis and insufficiency with total irregularity of the cardiac rhythm. Percussion note was dull over the right chest posteriorly. There were no rales. Tender liver edge was palpable three fingers breadth below the right costal margin. The diagnosis was circulatory insufficiency, auricular fibrillation, mitral stenosis and insufficiency.

II PATIENTS WITH SYPHILITIC HEART DISEASE

240 J P had had occasional slight pain below manubrium with attacks of shortness of breath. He felt weak and was unable to do hard labor. There was no history of congestive failure. Physical examination was negative except for a systolic murmur over the base. By x rays, aneurysm of the aortic arch was observed. The diagnosis was aneurysm of the aortic arch.

325 293, 276 J C had had shortness of breath, tired feeling, and nocturnal attacks of dyspnea and wheezing. There was no history of congestive failure. Dyspnea was unusually severe on the slightest exertion. Physical examination at time of first test showed marked arterial pulsations visible in the neck, a heaving apex impulse over the fifth space, left border of cardiac dulness 12.5 cm. from the midsternal line, systolic and diastolic murmurs over the apex and over the aortic area. The systolic murmur was transmitted into the vessels of the neck. Corrigan pulse was present. The lungs were clear, the liver was not palpable. Wassermann was positive at time of second test, no 293. Patient improved subjectively, and was able to walk about without shortness of breath. Physical examination was as noted before. At time of the third test, he had dyspnea on but slight exertion. He believed himself definitely worse than at time of previous tests. Physical examination was as before and showed no signs of congestive failure. The diagnosis was aortic insufficiency and syphilis.

326 P T entered the hospital complaining of paroxysmal dyspnea one year in duration. The attacks came mostly at night, were very severe, were accompanied by a choking sensation, lasted several hours and were not attended by pain. He had no swelling of the legs at any time. He had been working and when attacks were absent he felt normal. Physical examination showed left border of cardiac dulness 15 cm. from the midsternal line in the sixth interspace, double murmur over aortic area, Corrigan pulse. X ray showed dilatation of the arch of aorta. The vessels were sclerosed and tortuous. Kahn test was negative. The diagnosis was syphilis, aortic insufficiency, and aneurysm of aorta.

318 T P entered the hospital complaining of paroxysmal attacks of dyspnea, the attacks lasting for about a half an hour and at times accompanied by sensation of tightness over the chest. Attacks occur especially on excitement and on exercise. Physical examination showed a moderately enlarged heart with the signs of aortic insufficiency, and no signs of congestive failure. The diagnosis was syphilis, and aortic insufficiency.

316 M B entered the hospital complaining of shortness of breath. Although

he had suffered congestive failure in the past, and at the time of the test he was able to be up and about, he still complained of dyspnea on slight exertion. Physical examination showed a greatly enlarged heart with the signs of aortic insufficiency. The peripheral signs of aortic insufficiency were also present. No signs of congestive failure were present at the time of the test. The diagnosis was syphilis, and aortic insufficiency. Subsequent history. The patient died three and a half months later. He had shown signs of subacute bacterial endocarditis in the interval, as well as more conspicuous attacks of nocturnal paroxysmal dyspnea.

239, 243 W H had had for one year progressively increasing dyspnea, marked at night, and increasing weakness and cough for one month, and orthopnea for 2 weeks. Physical examination at the time of admission, one month before test no. 239, showed orthopnea, the apex of the heart in 6th space, left border of cardiac dulness 13 cm from midsternal line, and double murmurs over the aortic area. At the time of test, no. 239, there was orthopnea, no congestive failure and he was able to walk slowly on the level without becoming dyspneic. At the time of test, no. 243, his circulation was compensated fairly well at rest and on slight exertion. He felt definitely stronger. The diagnosis was aortic insufficiency and syphilis.

271 A S entered the hospital because of dyspnea and sharp, non-radiating pain in the right upper quadrant of five weeks duration. He noted swelling of the legs, and was troubled by cough. He was forced to use two or three pillows at night, but rapidly improved under rest and digitalis. Physical examination showed the sclerae slightly jaundiced and the heart in fifth space, 13 cm from midsternal line. Double murmur was heard over the aortic area and the tender edge of the liver was felt three fingers below the costal margin. There was no edema of the legs. The lungs were normal. He could walk on the level without stopping. Kahn test was positive. Fluoroscopy showed aneurysm of the ascending aorta. The diagnosis was aneurysm of ascending portion of the arch of aorta.

330 A J entered the hospital complaining of nocturnal dyspnea of fourteen months duration, and of dyspnea on the slightest exertion of four months duration. He had never suffered congestive failure. Physical examination at time of entry to hospital showed no signs of chronic passive congestion. The heart was moderately enlarged and there was a double murmur heard over the aortic area. The pulse was of the water-hammer type and Duroziez's sign was present. One week after entry, on the day of the test, he showed, for the first time, slight pitting edema of feet and ankles. Three days later, coincident with increasing congestive failure, he developed attacks of excruciating pain in the right upper quadrant. He became rapidly worse and died three days later. Post-mortem examination showed a heart weighing 700 grams, several old grayish scars in the myocardium and openings of the coronary arteries nearly obliterated by atheromatous changes in the aorta, which showed the characteristic signs of syphilitic involvement. The diagnosis was syphilis and aortic insufficiency.

III. PATIENTS WITH ARTERIOSCLEROSIS AND EVIDENCES OF MYOCARDIAL DEGENERATION

A With regular rhythm

371 J C entered the hospital on the surgical service where prostatectomy was performed. At time of test he complained of slight weakness. Physical examination was negative except for moderate tortuosity and sclerosis of peripheral vessels. The diagnosis was arteriosclerosis.

319, 332 N B entered the hospital because of osteomyelitis of the right first metatarsal bone. There was no history of circulatory embarrassment. Physical examination showed no signs of circulatory insufficiency, heart was normal in size, and tortuous and sclerosed brachial and temporal arteries. Urine was normal. The diagnosis was generalized arteriosclerosis.

361 A F entered hospital complaining of a painful left ankle which gradually became swollen, especially in morning after getting up. For several months he experienced some dyspnea on exertion. Physical examination showed the heart normal in size, sounds of fair quality, no murmurs, conspicuous sclerosis of the radial and tibial arteries, but no signs of circulatory insufficiency. The diagnosis was generalized arteriosclerosis.

370 H S entered the hospital because of a fractured femur. A diagnosis of Paget's disease was made. He complained of slight dyspnea on exertion. The heart was slightly enlarged, the radial and other superficial arteries conspicuously sclerosed and tortuous. There were no signs of circulatory incompetence. The diagnosis was Paget's disease, generalized arteriosclerosis.

372 389 J H collapsed while walking on street and entered hospital comatose. He gradually improved. He had been troubled with shortness of breath on exertion for several years. Physical examination showed the heart enlarged to the left, sounds fair, and a loud systolic murmur over the mitral area, no signs of circulatory insufficiency. Electrocardiographic tracings showed simple bradycardia. The diagnosis was bradycardia and generalized arteriosclerosis.

290 W L gave no history of congestive failure. Physical examination showed the heart normal in size. The sounds were of good quality and regular rhythm. Arteries were tortuous and thickened. The diagnosis was arteriosclerosis.

242 J B suffered from periodic attacks of constriction of the chest with epigastric pain and vomiting. Physical examination was negative except for marked arteriosclerosis. He was observed in one attack during which the electrocardiogram showed complete ventricular asystole of about 11 seconds duration. After discharge from the hospital, the patient showed almost daily attacks. He was unconscious during attacks. He had no signs of congestive failure. The diagnosis was Stokes-Adams syndrome, and myocardial degeneration.

295 M C complained of weakness of 6 months duration. He had frequently been troubled by painful joints for 15 years. Occasional palpitation with precordial pain was felt for several years which was associated with dyspnea on

exertion At time of test he was unable to walk more than 600 feet without conspicuous dyspnea There was no sign of congestive failure Physical examination showed marked emaciation Apex in fifth space was 9 cm from mid-sternal line The sounds were distant and regular There was slight tortuosity of peripheral arteries The diagnosis was myocardial degeneration and ? syphilis

241 D M felt tiredness and shortness of breath on walking for the past 2 years He gave no history of congestive failure Physical examination showed the heart normal in size The sounds were regular and distant Conspicuous thickening of the peripheral vessels was noted The diagnosis was marked generalized arteriosclerosis

284, 312 J G entered the hospital because of dyspnea, anorexia, and weakness beginning 4 weeks previous to this test, when he developed severe attacks of nocturnal dyspnea, associated with a sense of pressure over the epigastrium Physical examination showed orthopnea The sounds were faint A soft systolic murmur over the aortic area was heard Brachial and radial arteries were sclerosed Moist râles over both bases were heard The liver edge was palpable and tender Slight pitting edema over both ankles was present At time of second test, no 312, the patient was objectively and definitely worse He was able to sleep flat on the right side though not on the left side, and was still troubled by paroxysmal nocturnal dyspnea Physical examination was as before except that there was a presystolic gallop rhythm and moist râles could be heard everywhere over both lungs There was marked pitting edema over the buttocks, the thighs and legs, and his face and arms were edematous The diagnosis was arteriosclerosis and cardiac asthma

360 M H entered the hospital complaining of increasing shortness of breath and swelling of the feet, twelve months in duration At time of test he was orthopneic Physical examination showed an enlarged heart with the maximum impulse in the sixth space 13.5 cm from the midsternal line The first sound was snapping and was followed by a soft systolic murmur Conspicuous swelling and pitting edema of legs and signs of fluid in the right chest were found Liver was not palpated The patient's course was progressively downward and he died two weeks later The diagnosis was generalized arteriosclerosis, and ? syphilis

341 T R entered the hospital with conspicuous dyspnea, weakness and discomfort At time of test there was no orthopnea although his dyspnea was extreme The size of the heart was approximately normal and no murmurs were heard The rate was rapid and regular There were signs of fluid in the abdomen and in the right chest Marked pitting edema was noted over the extremities The diagnosis was myocardial degeneration and general anasarca

B With fibrillation of the auricles

362 M C entered the hospital complaining of palpitation and dyspnea eleven months in duration Physical examination showed the left border of cardiac dulness 14 cm from the midsternal line in the fifth interspace The heart sounds were totally irregular There was slight pitting edema over the ankles The diagnosis was auricular fibrillation and arteriosclerosis

411 M M entered complaining of shortness of breath and palpitation. On entry to hospital he showed the signs of congestive failure which responded well to treatment by rest and digitalis, so that at the time of test there was but slight pitting edema over the legs. The heart was slightly enlarged. No râles were heard over the lungs. The diagnosis was auricular fibrillation and generalized arteriosclerosis.

246, 261 W D, five years previously, following an operation, had shortness of breath, slight orthopnea, and swelling of legs and abdomen. Diagnosis at that time was auricular fibrillation, chronic myocarditis, coronary sclerosis and ascites. One week before admission he noted swelling of the ankles. At time of test no 246, he had been completely digitalized and showed evidence of mild toxic effects such as vomiting. Physical examination showed the heart rhythm totally irregular, and the left border of dullness 13 cm. from the midsternal line in the fifth space. Bubbling râles were heard over bases of lungs. He was short of breath and unable to walk. The liver edge was palpable and tender. He showed slight pitting edema over the ankles and of subcutaneous tissues. At time of test no 261, there was no edema of the legs. Vital capacity was not reliable because of nasopharyngitis. The diagnosis was myocardial degeneration, auricular fibrillation.

247 F B had dyspnea on moderate exertion and nocturnal paroxysmal attacks of precordial distress associated with shortness of breath. There was no history of congestive failure. Physical examination showed heart apex impulse in the fifth space, 11.5 cm. from the midsternal line. Sounds were distant. There was marked sclerosis of the peripheral vessels. The diagnosis was auricular fibrillation, arteriosclerosis and cardiac asthma.

IV PATIENTS WITH ARTERIAL HYPERTENSION

377 T M had never complained of any symptoms referable to his cardiovascular system. Physical examination showed the heart slightly enlarged. The sounds were normal and regular in rhythm. The diagnosis was essential hypertension.

272 E M had had attacks of dizziness, forcing him to lie down. These were associated with pain over the lower anterior chest, and palpitation. There was no swelling of ankles or puffiness of face. Physical examination showed tortuous retinal vessels, the left border of cardiac dullness 9.5 cm. in the nipple line in the fifth space. The pulses were equal, regular and synchronous, and the radial arteries neither thickened nor sclerosed. Blood pressure during stay in hospital varied from 170 to 200 systolic and from 110 to 140 diastolic. Urine showed a specific gravity of 1004, no fixation, slight trace of albumin, no sugar and numerous red cells. Phthalein test of kidney function showed 57 per cent the first hour and 21 per cent the second hour. Wassermann test was negative. The diagnosis was hypertension and vascular nephritis.

307 B M had had for 6 years dizziness and headaches but no symptoms of cardiac decompensation. He had had arterial hypertension for at least 5 months. Physical examination showed puffiness about both eyes. The heart was enlarged to the left and a soft blowing systolic murmur was heard over apex. Lungs

were clear Liver was not felt Blood pressure at first determination, 5 months previously, was 188 systolic, and 90 diastolic Urine was negative The diagnosis was hypertension

331 F S entered the hospital complaining of shortness of breath two months in duration He was dyspneic, and orthopneic on entry, and showed edema of both legs After five weeks of rest in bed in the hospital he improved so that at the time of test he was neither orthopneic or dyspneic, and showed no evidence of congestive failure Physical examination showed a slightly enlarged heart and slight arteriosclerosis Kahn test gave a negative reaction The diagnosis was hypertension

357 G M stated that his high blood pressure had been accidentally discovered one year previously He felt well and had been actively at work Physical examination showed the heart slightly enlarged The anterior posterior diameter of the chest seemed somewhat increased, and an occasional musical râle could be heard on expiration The diagnosis was hypertension and ? pulmonary emphysema

336 A O entered the hospital because of carcinoma of lip His elevated blood pressure was discovered in the course of the routine physical examination No symptoms were referable to the cardiovascular system Physical examination showed slight cardiac enlargement and moderate thickening of the arteries and veins The diagnosis was hypertension

309 J M had had dizziness of 7 months duration but no dyspnea, orthopnea, or evidence of congestive failure Nocturia 3 had been present for 7 months Physical examination showed the apex impulse in fifth space, 12 cm from the midsternal line The heart rate and rhythm were normal and no murmurs were heard Urine showed no fixation of specific gravity and very slight trace of albumin The diagnosis was hypertension

305 H M had had occasional shortness of breath of 2 weeks duration, and a choking sensation the night before admission He had had several similar attacks during the previous 2 months but no symptoms of congestive failure There had been nocturia 2-3 of one month's duration Physical examination showed edema of conjunctivae and eyelids, and the heart, moderately enlarged The sounds were regular and of fair quality No murmurs were heard There was no evidence of sclerosis Non-tender liver edge was palpable two fingers below costal margin There was no orthopnea Urine showed no fixation of gravity, and a slight trace of albumin There was no nitrogen retention, no signs of arteriosclerosis or congestive failure The diagnosis was hypertension

296, 300 M P, beginning 5 years before entry, had had attacks of pain in chest radiating to left arm, associated with dyspnea Three weeks before entry, paroxysms of pain and dyspnea became more frequent and more severe Paroxysms lasted about 3 minutes and were agonizing Physical examination showed peripheral vessels sclerosed and tortuous, heart not enlarged and no signs of congestive failure Urine showed a slight trace of albumin and hyaline casts with a slight tendency toward fixation of specific gravity The diagnosis was hypertension and chronic nephritis

308 M C had had precordial pain of several years duration, with occasional palpitation. Patient never stopped his work. There was no dyspnea or orthopnea and no evidence of congestive failure. Physical examination showed heart apex in fifth space, 12 cm from the midsternal line, no murmurs and no thrills. The lungs showed the signs of emphysema. Liver was not felt. Radial and brachial arteries were sclerosed and somewhat tortuous. There were no signs of congestive failure. Urine was entirely normal with no fixation of gravity. The diagnosis was arteriosclerosis and hypertension.

304 M S had no cardiac history but was troubled by dizziness and headaches. Hypertension was discovered accidentally. Physical examination was entirely normal. Urine was clear with no fixation of specific gravity. There was no nitrogen retention. The diagnosis was hypertension.

427, 429 C B had noticed slight dyspnea on exertion beginning two years before entry which had gradually become progressively worse. His blood pressure had been elevated for at least three years. Three weeks before entry his feet and legs began to swell. Physical examination at the time of the first test showed conspicuous congestive failure with cyanosis and dyspnea. There was generalized anasarca. The heart was moderately enlarged. His weight was 162 pounds. The patient was rapidly digitalized and within twelve hours passed large amounts of urine, his ventricular rate slowed, and his vital capacity increased. His weight at the time of the second test was 146 pounds. The edema had lessened conspicuously, though light pitting edema was still evident over the lower extremities and the buttocks. The diagnosis was hypertension, cardiac decompensation.

423 P F had never been troubled by symptoms referable to his cardiovascular system, but on rest in bed first developed swelling of the legs. Physical examination was negative save for the elevated blood pressure and edema of the legs. The diagnosis was hypertension.

278 J G had had attacks of abdominal pain, and frequent attacks of severe nocturnal dyspnea, lasting 10 to 15 minutes. Heart was normal in size, sounds regular and of good quality. Faint systolic murmur over the mitral area. Pulses were equal and of increased tension. Liver edge was felt 3 fingers below the costal margin, moderately tender. There was no edema over the extremities. Urine showed a tendency toward fixation of specific gravity, slight trace of albumin, occasional hyaline and cellular casts. There was no nitrogen retention. Phthalein output was 45 per cent in 2 hours. The diagnosis was hypertension, vascular nephritis.

334 E A had suffered a complete right hemiplegia two years previously from which he had only incompletely recovered. For sixteen months he had suffered from shortness of breath on exertion with nocturnal dyspnea, of one month duration. He had known that his blood pressure was elevated for two and a half years. Physical examination showed sounds of poor quality, rapid, and absolutely irregular in rhythm. No murmurs were heard. The radial arteries were thickened. The diagnosis was auricular fibrillation, arteriosclerosis and hypertension.

CLINICAL STUDIES ON THE VELOCITY OF BLOOD FLOW

X THE RELATION BETWEEN THE VELOCITY OF BLOOD FLOW, THE VENOUS PRESSURE AND THE VITAL CAPACITY OF THE LUNGS IN FIFTY PATIENTS WITH CARDIOVASCULAR DISEASE COMPARED WITH SIMILAR MEASUREMENTS IN FIFTY NORMAL PERSONS¹

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In preceding papers, particular attention has been directed to the relation in a given individual or in a group of individuals between the clinical findings and the measurements of the velocity of blood flow, the venous pressure, and the vital capacity of the lungs. In the following, more general treatment of the data, an attempt will be made to learn the extent and frequency of changes in these measurements in all subjects with cardiovascular disease compared with similar measurements in normal persons.

Changes in the venous pressure, in the velocity of blood flow, and in the vital capacity of the lungs can be compared with each other only if obtained in the same subjects. Such comparison would be almost certainly erroneous, if, for example, variations of venous pressures of some patients with cardiovascular disease were compared with variations of the vital capacities of other patients with cardiovascular disease, for it would be impossible to be certain that such different groups showed exactly the same degree of cardiovascular damage. Consequently, we have included here only those patients in whom all three measurements were obtained. Duplicate measurements in the same subject have been excluded in order not to weight some of the results unduly. Fortunately, the three measurements in all but four patients with cardiovascular disease, and the data in

¹ This investigation was aided by a grant from the DeLamar Mobile Research Fund of Harvard University.

all but twelve normal individuals are available. The fifty normal persons are those presented in the study of the normal pulmonary circulation time (1), the fifty patients with cardiovascular disease are those included in the preceding communication (2).

Since measurements of the velocity of blood flow, of the venous pressure, and of the vital capacity of the lungs are expressed in such dissimilar units as seconds, centimeters of water, and cubic centimeters of air per square meter of body surface, since the order of magnitude of the measurements differs widely, and since, moreover, the vital capacity diminishes, the venous pressure rises, and the pulmonary circulation time and the arm to heart time becomes greater in circulatory insufficiency, comparison of such unlike quantities is difficult. All measurements have, therefore, been reduced to a common basis by expressing them in terms of percentage variation from their normal average. In all diagrams (see fig. 1) the measurements have been classified in 10 per cent groups. The shaded columns, for example, between +5 and -5 indicate the number of subjects in whom the measurements were found to be within the limits of +5 and -5 per cent of the average of the entire normal group. Vital capacity measurements were first expressed in the number of cubic centimeters per square meter of body surface. The percentage of the normal average was then calculated. If, for example, the vital capacity of a given individual was 1782 cc per square meter of body surface, and the normal average 2376 cc per square meter of body surface, the vital capacity observed would be 75 per cent of the normal, or, as we have charted it, a percentage deviation from the normal of -25 per cent. Similarly, the actual venous pressure has been calculated in terms of percentage of the average normal and the variation of this percentage from the normal charted.

Expression of the pulmonary circulation time and of the arm to heart time in terms of actual velocity presented a somewhat different problem. The "circulation time" denotes the time necessary for a substance to travel between two arbitrarily fixed points, the longer the time necessary, the slower is the speed of the substance. To express this inverse relation between circulation time and velocity it has been necessary to divide the average normal pulmonary circulation time by the one observed in order to secure an estimate of the

speed in terms of the normal percentage. The normal average pulmonary circulation time is eleven seconds, and if, for example, the observed time in a patient with cardiovascular disease were twenty-two seconds, the doubling of the circulation time denotes a slowing of the blood stream to one-half the normal average velocity. A circulation time of twenty two seconds would therefore be charted as -50 per cent. The data relating to the arm to heart times have been similarly treated.

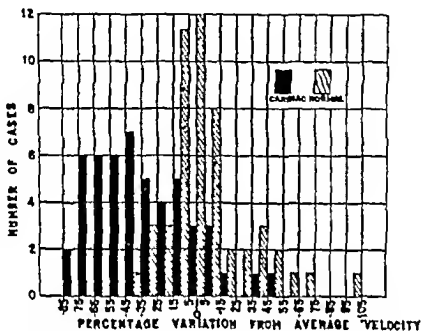


FIG 1 PULMONARY CIRCULATION TIMES (CRUDE) OF NORMAL AND CARDIAC SUBJECTS

In these diagrams the normal measurements are those obtained in the fifty subjects we personally studied, and the data in patients with cardiovascular disease are those presented in the preceding communication. The methods employed and the conditions of the tests were consequently similar. The group of patients with cardiovascular disease includes those whose circulation was compensated, as well as those whose circulation was insufficient. The patient with cardiovascular disease in whom the velocity of blood flow (plus 47 per cent) was swiftest, for instance, showed essential hypertension and had never experienced symptoms or signs of circulatory insufficiency.

The frequency distribution of the pulmonary circulation time (crude)

The diagram (fig 1) shows the degree and frequency of variations in the pulmonary circulation times in fifty patients with cardiovascular disease compared with the findings in fifty normal persons. A frequency distribution diagram such as the one presented is of value in showing the degree and incidence of variations in the velocity of blood flow in cardiovascular disease compared to the normal. For purpose of diagnosis, the ideal test would be one according to which all results in diseased states differed from any found in normal sub-

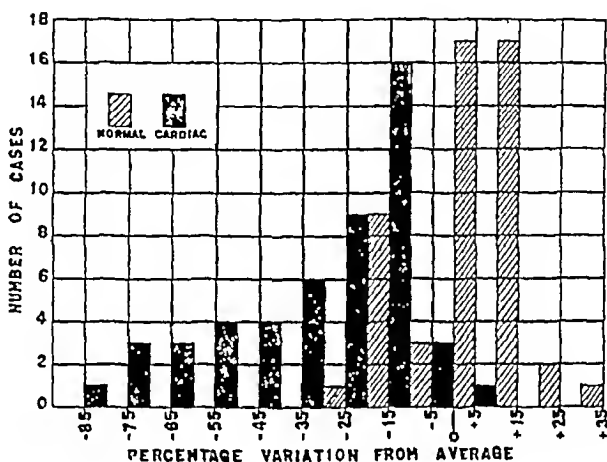


FIG 2 COMPARISON OF THE VITAL CAPACITIES OF CARDIAC AND NORMAL SUBJECTS

jects. The degree to which a test approaches this ideal is one measure of its diagnostic importance. It is consequently of interest that of the fifty patients with cardiovascular disease, twenty showed more marked diminution in the velocity of pulmonary blood flow than that found in any single normal subject of this series.

The frequency distribution of the vital capacity of the lungs (per square meter of body surface)

The percentage variation in the normal subjects and in patients with cardiovascular disease has been charted (fig 2). In the nor-

mal subjects the range of their vital capacity variations is less than that of their pulmonary circulation times, but it should be noted that in the cardiovascular patients likewise there is a similar relation, the deviation from the normal average pulmonary circulation time is correspondingly less striking. Although twenty cardiac patients showed more marked diminution in the velocity of pulmonary blood flow than that found in the lowest normal subject (fig 1), in the vital capacity, only fifteen patients showed more marked diminution than the lowest normal.

The frequency distribution of the arm to heart times

The diagram (fig 3) shows the degree and frequency of variation in the arm to heart times in fifty patients with cardiovascular

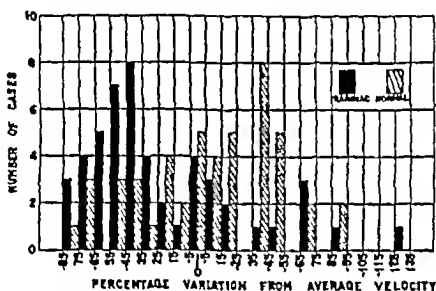


FIG 3 COMPARISON OF ARM TO HEART TIMES OF CARDIAC AND NORMAL SUBJECTS

disease compared with the findings in fifty normal persons. In contrast to the measurements of the vital capacity and of the pulmonary circulation times, the normal arm to heart times show a much greater variation (fig 3). While the normal vital capacities of the lungs per square meter varied over a range of 70 per cent and the pulmonary circulation times, with one exception, over 120 per cent, the arm to heart times of normal persons varied over a range of 180 per cent. Not only is the spontaneous variation of the arm to heart time in normal subjects great, but the variation in cardiovascular subjects

is practically identical except that the incidence of the increased times (diminished velocity) is somewhat greater in cardiovascular disease. This finding of such great difference in the normal arm to heart time is in harmony with the studies of G. N. Stewart (3), and Hewlett and Van Zwaluwenburg (4) who observed that the volume flow of the arm varied considerably.

The frequency distribution of the venous pressure

Inspection of the chart (fig. 4) which compares the venous pressures of the fifty patients with cardiovascular disease with the venous pressures in normal persons shows that in both groups of subjects the

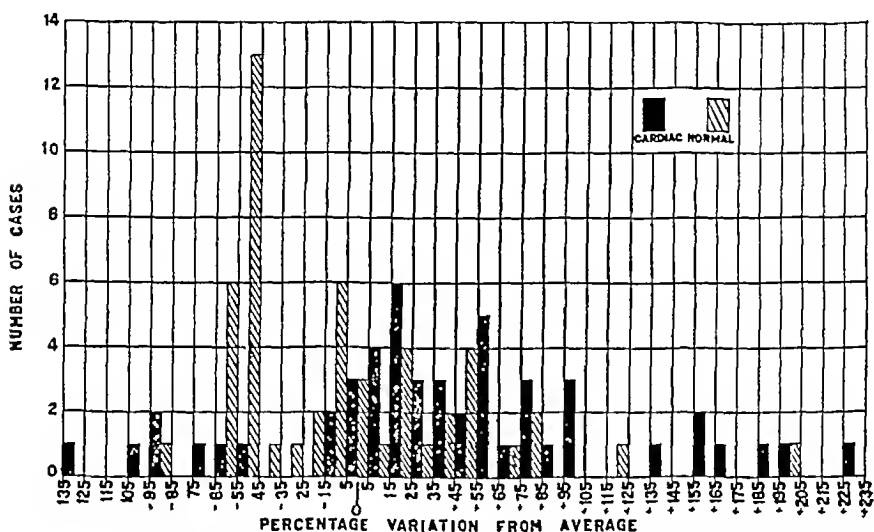


FIG. 4. COMPARISON OF VENOUS PRESSURES OF CARDIAC AND NORMAL SUBJECTS

variability is far greater than that shown by the other measurements. The venous pressure in cardiovascular disease varied over a range of some 360 per cent, in normal subjects over some 300 per cent. Of the fifty normal subjects, thirty showed a venous pressure below the average, twenty, a venous pressure above the average. In cardiovascular disease twelve measurements were below the average, thirty-eight above the average. Analysis of these findings confirms our general impression that the stage of congestive failure is attended

by a significant rise in venous pressure, but that this rise cannot be interpreted as diagnostic because of the great variability shown by normal persons

The relation of the pulmonary circulation time (crude) to the weight and height

In the foregoing discussion of the vital capacity of the lungs and of the crude pulmonary circulation time, the former has been reduced to the number of cubic centimeters per square meter of body surface, whereas the crude pulmonary circulation time used in the computa-

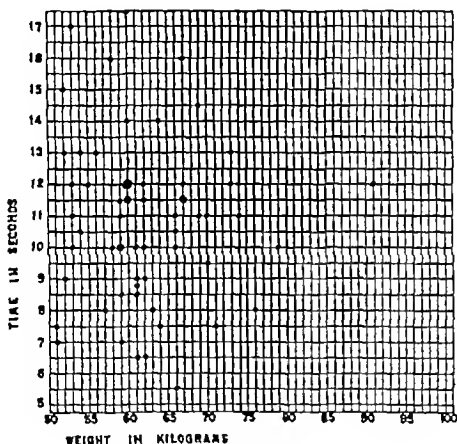


FIG 5

tions has been the one actually observed at the time of test. In order to learn whether the pulmonary circulation time in normal persons varies according to the weight or to the height, diagrams have been made (fig 5, fig 6). According to these diagrams the variation in the crude pulmonary circulation time is as great when referred to weight or height, as when the actual observed time is charted. The

circulation time as used in this connection refers to the time necessary for the radium active deposit to travel from the right auricle to the left antebrachial artery. That the time of transit is essentially the same in all individuals regardless of height or weight indicates that the velocity of blood flow in different sized individuals varies in such a way as to maintain in general the same time of transport.

The relation of the crude pulmonary circulation time to the vital capacity of the lungs in normal persons and in patients with cardiovascular disease

The frequency distribution of the vital capacity and of the crude pulmonary circulation time discussed earlier in this communication

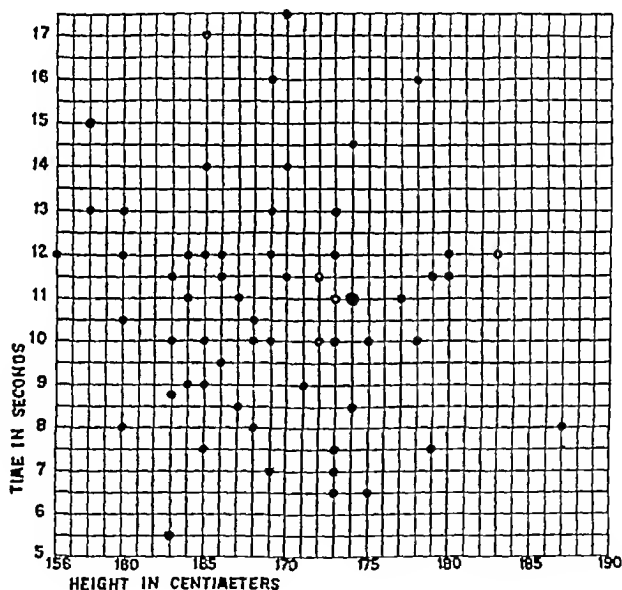


FIG 6

does not indicate whether those individuals who showed a lower vital capacity tended to show a greater pulmonary circulation time (decreased velocity). To study the relationship between the pulmonary circulation time and the vital capacity of the lungs more clearly, a diagram (fig 7) has been constructed. The chart is divided into four parts by a vertical and a horizontal line. The horizontal line

represents the average normal pulmonary circulation time. The vertical line represents the average normal vital capacity found in our fifty normal persons. Group 1 consists of individuals in each of whom a low pulmonary circulation time was associated with an increased vital capacity, group 2, of persons in each of whom a low pulmonary circulation time was associated with a lowered vital capacity, group 3, of persons in whom a prolonged pulmonary circulation time was associated with an increased vital capacity, and group 4, of persons in whom a diminished vital capacity was associated with a prolonged pulmonary circulation time (decreased velocity). The normal subjects of each group are included in the smaller squares, the subjects with cardiovascular disease, in the larger squares. The normal subjects are distributed fairly evenly into the four groups so that the probability of a given normal individual being in any one group is about equal. Quite the reverse is true of patients with cardiovascular disease. They show a striking tendency to be in group 4 (prolonged pulmonary circulation time and decreased vital capacity).

According to the results shown in figure 7, the probability of a given individual with a low vital capacity (groups 2 and 4) having cardiovascular disease could be expressed by

$$\frac{\text{Group 2 cardiovascular plus Group 4 cardiovascular}}{\text{Group 2 normal plus Group 4 normal}}, \text{ or } \frac{45}{21}$$

That is to say, roughly, the probability, regardless of the pulmonary circulation time, would be two to one. Similarly if the pulmonary circulation time were prolonged (groups 3 and 4), indicating a slower velocity of pulmonary blood flow, the probability of the subject having cardiovascular disease regardless of the vital capacity of the lungs would be $\frac{41}{21}$, or again, roughly two to one. If, however, both tests were performed and the pulmonary circulation time were found prolonged and the vital capacity diminished (group 4), the probability of the subject having cardiovascular disease would be expressed by

$$\frac{\text{Group 4 cardiovascular}}{\text{Group 4 normal}} \text{ or } \frac{40}{9}, \text{ or approximately four to one}$$

This indicates that changes in the pulmonary circulation time occur simultaneously with changes in the vital capacity of the lungs.

The relation of the venous pressure to the crude pulmonary circulation time and to the vital capacity of the lungs

When, in addition to changes in the vital capacity of the lungs and the pulmonary circulation time, alterations of the venous pressure are compared to the other two measurements, a diagram similar to figure 7 can be constructed in which there are eight squares Figure 8

<p>GROUP I PCT- VC +</p> <p>CARDIOVASCULAR SUBJECTS</p> <p><u>1</u></p>	<p>GROUP II PCT. - VC. -</p> <p>CARDIOVASCULAR SUBJECTS</p> <p><u>5</u></p>
<p>GROUP III PCT.+ VC. +</p> <p>CARDIOVASCULAR SUBJECTS</p> <p><u>1</u></p>	<p>GROUP IV PCT.+ VC. -</p> <p>CARDIOVASCULAR SUBJECTS</p> <p><u>40</u></p>

GR I
NORMAL
SUBJECTS
10

GR II
NORMAL
SUBJECTS
12

12
NORMAL
SUBJECTS
GR III

8
NORMAL
SUBJECTS
GR IV

FIG 7

<p><u>4</u></p> <p>NORMAL SUBJECTS</p> <p>PCT.+ VC. - VP +</p>	<p><u>31</u></p> <p>CARDIOVASCULAR SUBJECTS</p> <p>PCT. + VC. - VP +</p>
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FIG 8

represents one square in which those persons are found in whom a high venous pressure was associated with a diminished vital capacity of the lungs and a prolonged pulmonary circulation time. This square is analogous to the group 4 square of figure 7. Only four normal subjects satisfy these requirements in contrast to the thirty-one subjects with cardiovascular disease. If, consequently, a given person shows increased pulmonary circulation time, decreased vital capacity of the lungs, and venous pressure above the average normal, the probability of his having cardiovascular disease would be eight to one. It should be noted, however, that although the probability of a person with cardiovascular disease being in the group (group 4, fig. 7) with decreased vital capacity and prolonged pulmonary circulation time would be four out of five, 40/50, the probability of his being in the group (fig. 8) which showed in addition an increased venous pressure would be only three out of five, 31/50. Consequently, if a subject shows such changes (shown in fig. 8) from the normal, the probability is great that he has cardiovascular disease while if he fails to show such changes, the significance is not so great for he may be one of the 40 per cent group of patients with cardiovascular disease that does not show such deviations.

Statistical study of data such as is presented in this communication is important in physiological study of the dynamics of the circulation for it throws considerable light on the general relation between the velocity of blood flow, the vital capacity of the lungs and the venous pressure under both normal and pathological conditions. In an individual instance these considerations are of limited interest. It is not for a moment proposed that such formulae should be used in the diagnosis and prognosis of circulatory disease. These will, in fact, usually depend on the physical examination and history. On the other hand, the general knowledge of the velocity of the peripheral and pulmonary blood flow in different types of cardiovascular disease is of considerable value both physiologically and clinically. In certain obscure cases the electrocardiograph and the vital capacity of the lungs give useful information and it is felt that the measurement of the velocity of blood flow may, similarly, be of value since it affords a more direct measurement of the cardiac and vascular response in appropriate pathological conditions. Later communications will

show that knowledge of the velocity of blood flow in normal persons and in patients with circulatory insufficiency affords a basis for study of the adaptations of the circulation in conditions such as fever, anemia, hyperthyroidism and myxedema, as well as of the effects of various drugs upon the circulation

We are indebted to Dr E B Wilson for his assistance in the statistical analysis of the data

SUMMARY AND CONCLUSIONS

The relation between the pulmonary circulation time, the arm to heart time, the venous pressure, and the vital capacity of the lungs in fifty patients with cardiovascular disease has been compared with similar measurements in fifty normal subjects

1 All measurements were expressed in terms of the percentage deviation from the normal average Of the fifty patients with cardiovascular disease, twenty showed more conspicuous slowing of the pulmonary blood flow than that observed in any of the fifty normal subjects, while only fifteen patients showed more marked diminution in the vital capacity of the lungs than that found in any normal subject

2 The arm to heart times of normal subjects and of patients with cardiovascular disease showed a greater percentage variation (from the normal average) than the vital capacity of the lungs and the pulmonary circulation time The variations in normal subjects are over the same range as in disease but the incidence of the increased times (diminished velocity) is greater in cardiovascular disease

3 Of the four measurements, the venous pressure showed the greatest variability both in normal subjects and in patients with cardiovascular disease The variation in normal subjects was over the same range as in patients with cardiovascular disease although, in general, the stage of congestive failure was attended by a significant rise above the level of normal

4 Unlike the vital capacity of the lungs, the pulmonary circulation time and the arm to heart times bear no relation to the weight, to the height, or to the surface area of the subjects

5 In normal subjects the variations in the vital capacity of the lungs

are independent of variations in the pulmonary circulation time so that if the measurements are grouped according to their deviation from the average, the probability of a given normal subject being in any of the four groups is about equal

6 In cardiovascular disease, however, there is a striking tendency for a decrease in the vital capacity of the lungs to be associated with an increase of the pulmonary circulation time which denotes a slower speed of blood flow through the lungs

7 Statistical study of our measurements shows that, in a given person, if the vital capacity of the lungs is below the average normal the probability of his having cardiovascular disease is roughly two to one

8 Statistical study of our measurements shows similarly that in a given person, if the pulmonary circulation time is above the average of normal the probability of his having cardiovascular disease is roughly two to one

9 If a given individual has both a low vital capacity and an increased pulmonary circulation time, the probability, according to our experience, of his having cardiovascular disease would be four to one

10 If, in addition to retardation in the pulmonary blood flow (increased pulmonary circulation time) and to diminution in the vital capacity of the lungs, the subjects show venous pressure increased above the normal average, the probability of his having cardiovascular disease is roughly eight to one

11 It should be noted, however, that whereas the probability that a person with cardiovascular disease is in the group with a decreased vital capacity and increased pulmonary circulation time is four to one, the probability when he shows also increased venous pressure, is but three to one

12 The value and limitations of the statistical analysis of the data are pointed out

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THE DETERMINATION OF THE CIRCULATING BLOOD VOLUME WITH CARBON MONOXIDE

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INTRODUCTION

The estimation of the circulating blood volume in man is of interest in the study of a number of clinical problems. The results published by many investigators have varied widely. The principle involved in all of these studies consists in the introduction into the blood stream of a measured amount of some substance whose concentration in the circulating blood may then be estimated after complete mixing has taken place. Many materials have been employed and the literature has been reviewed in recent articles (1, 2). The type of substance most commonly used has been a dye whose concentration in the blood plasma is estimated with a colorimeter. The dye chiefly used is vital red, concerning which a considerable literature has appeared (3). The objections which have been raised to the use of dyestuffs may be briefly stated. Quantitative intravenous injection without extravasation is frequently difficult. Injections have been followed by serious reactions. Considerable losses may occur from the plasma through adsorption on the erythrocytes, removal by phagocytosis, and by diffusion into the lymph and other body fluids. Where alterations in capillary permeability occur in pathological conditions, as in edema, considerable amounts may penetrate rapidly into the tissues (4). For accurate colorimetric observations precautions must be taken to have the plasma clear and free from hemoglobin.

A recent reinvestigation of the problem by Lindhard appears to have revealed other difficulties. After the injection of the dye into a peripheral vein, an appreciable time interval is needed to allow complete mixing throughout the circulation. It now appears that com

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plete mixing does not take place in the blood stream in the three or four minutes usually allowed (5) If the subject exercises by walking and by making arm movements for a period of ten minutes after the dye injection, much lower results than have previously been reported by this method are obtained for the blood volume As any loss of the injected dye from the blood during this period should make the apparent blood volume higher, not lower, these findings indicate that previous workers have not secured the necessary complete mixing in the circulating blood It is further claimed that if a series of determinations are made on one individual, as is highly desirable if not indispensable in clinical studies, tolerance is produced, so that the dye disappears with increasing rapidity from the blood after four or five successive blood volume determinations are made Larger apparent blood volume values are then obtained with each subsequent determination This finding is at variance with the extraordinarily constant values which have been reported by others when repeated determinations of the blood volume by the dye method have been made on one individual over a considerable period (6)

The use of carbon monoxide possesses certain advantages which deserve consideration We have particularly in mind its employment in those conditions in which the capillary permeability may be altered, and where the diffusion of dyestuffs from the plasma into the tissue spaces may be greatly accelerated They include many of the pathological conditions in which blood volume changes may be expected and are of particular interest The carbon monoxide method was first used in its present form by Haldane and Smith (7), and improvements were made by Douglas (8), and by Salvesen (9), working in Van Slyke's laboratory

Carbon monoxide in sufficient amounts may be quantitatively introduced into the blood by inhalation without pain or danger The method of introduction into the minutely divided blood stream in the lung capillaries greatly facilitates diffusion and rapid, complete mixture The gas by reason of its affinity for hemoglobin is entirely bound, for all practical purposes, to this substance alone The amount which is physically dissolved in other tissues is insignificant By the gas methods described below its estimation in small quantities of blood is easily and accurately made

The calculation of the blood volume and of the total hemoglobin is then easily made. Knowing the amount of gas absorbed and its concentration in the blood after mixture, the blood volume is readily obtained. If the oxygen capacity is known the concentration of hemoglobin may be estimated. The blood volume multiplied by this figure will then give the total circulating hemoglobin.

METHOD OF ADMINISTERING CARBON MONOXIDE

The method employed for the administration of the gas is essentially that used by Haldane and followed by subsequent observers. A rebreathing apparatus is used consisting of a small rubber bag with glass connecting tube and rubber mouthpiece. In unconscious persons a mask with minimal dead space is used instead. The bag is filled with air and after rebreathing has commenced a measured amount of carefully purified carbon monoxide is added from a gas burette. The subject breathes back and forth into this bag through a small bottle filled with fresh soda lime to remove carbon dioxide. The bottle is placed in an ice filled jacket, in order to cool the air and to precipitate excessive moisture. Care is taken to have the total amount of gas in the bag as small as possible so that at the height of inspiration it is nearly collapsed. Oxygen is admitted to it very slowly in amounts just sufficient to balance absorption from a large pressure tank, equipped with a needle valve. The dead space is thus reduced to a minimum. The concentration of oxygen in the bag does not exceed 30 per cent. As the tension of carbon monoxide in the blood depends on the corresponding partial pressure of oxygen, this precaution is necessary in order that the carbon monoxide may be absorbed as completely as possible in the lungs. The total volume of the gas in the system at the moment of complete normal expiration does not usually exceed 2500 cc. A side tap is placed in the connection between bag and absorber so that a sample of gas may be taken just before the conclusion of the experiment or whenever desirable, to check the concentration in the bag. Before such a gas sample is to be removed, the oxygen supply is completely shut off and ten or twelve respirations into the closed system are taken in order to obtain complete mixture of gas between lungs and apparatus.

The subject breathes to and fro into the bag for a period of twenty

minutes. At the end of this time a blood sample without stasis is taken from an arm vein. Aside from the venapuncture, no pain or discomfort whatever is experienced.

METHOD OF ANALYZING BLOOD SAMPLES

The blood samples for carbon monoxide analysis are collected in oiled syringes and placed in bottles containing dry oxalate under oil. The samples are analyzed without delay.

We have employed two methods for the analysis. The first is an elaboration of the procedure used by Barcroft and his associates (10). An accurately measured 5 cc sample of the thoroughly mixed blood is introduced into the extraction chamber of a Van Slyke constant pressure apparatus and 15 cc of completely extracted acid ferricyanide solution are added. After the solution is shaken for twenty minutes, the liquid is removed as far as possible into the side arm of the apparatus, and the extracted gas (about 3 cc) is transferred with several washings into a Krogh gas analysis apparatus of suitable construction provided with a combustion chamber. Estimations of the carbon monoxide are made with an accuracy of about 0.005 per cent. A comparison of the volume of carbon monoxide lost in combustion is then made with the volume of carbon dioxide formed. The agreement is usually very close. The temperature is estimated with a thermometer suspended in the water bath surrounding the gas pipette and thermobarometer. The total volume of carbon monoxide present, corrected by the addition of the amount left dissolved in the fluid from which it was extracted (as calculated from the basic equation of Van Slyke, 1924) (11), is then readily obtained.

The second method is that of Van Slyke and Robbins (12) to which our attention was kindly drawn by Dr. Van Slyke after the above procedure was elaborated and in use. This also requires the use of a 5 cc blood sample, which is analyzed by the absorption of oxygen (pyrogallol) and then of carbon monoxide (Winkler's reagent) in the Van Slyke-Harrington constant volume pipette. The agreement of results obtained by these two different procedures is satisfactory (Table 1). Calibration of the Van Slyke-Harrington pipette for this determination requires care, the final volume read being 0.5 cc.

We have made a number of blood volume estimations upon normal

TABLE 1

Comparison of results obtained by extraction and combustion analysis with those obtained by the method of Van Slyke and Robbins

	Extraction in vacuo and combustion	Van Slyke-Robbins method
1	2 62	2 63
2	2 55	2 54
3	1 79	1 85
4	2 08	1 98
5	2 59	2 59
6	2 33	2 25
7	2 25	2 25
8	2 34	2 35
9	1 34	1 42
10	3 09	3 11
11	2 68	2 58
12	1 63	1 68
13	2 23	2 26
14	1 44	1 48

TABLE 2

Blood volume of normal young men and young women—ages 23 to 35 years

(All of these determinations were made in the months of December January and February in the early afternoon, about one hour after a light lunch.)

Number	Subject	Sex	Weight	Circulating blood volume	Blood volume		Red blood cells	Oxygen capacity	Cell volume
					cc. per kg. m weight	cc. per sq. m surface			
			kgm.	cc			millions per cu. mm.	volumes per cent	per cent
1	W	M	72.4	4,690	64.8	2,510	4.8	18.4	40.0
2	G. G.	M	67.0	4,720	69.6	2,660	5.8	20.8	42.0
3	D	M	87.3	5,610	64.9	2,690	4.9	21.0	42.0
4	E. H.	M	71.4	5,410	75.5	2,860	4.4	20.2	40.8
5	E. H. H.	M	73.6	4,740	64.4	2,550	5.3	20.6	43.5
6	H. C.	M	65.8	4,710	71.5	2,720	5.1	20.7	39.5
7	W. A. P.	M	75.4	4,760	63.4	2,540	5.0	18.1	40.5
8	B. L.	M	83.1	5,260	63.4	2,710	5.8	20.8	42.5
9	C. K.	F	55.6	3,455	64.5	2,200	4.3	18.0	40.0
10	E. N.	F	52.6	3,460	65.7	2,380	4.5	19.1	41.0
11	L. W.	F	51.1	3,618	71.8	2,365	4.6	17.8	39.5
12	R.	F	53.4	3,415	65.4	2,280	4.7	20.4	43.0
13	DeH.	F	50.7	3,360	69.0	2,385	4.1	19.2	39.5
14	S.	F	54.8	3,185	60.4	1,990	4.6	18.3	40.2
15	N	F	58.6	3,680	62.8	2,260	4.4	20.9	41.5
16	Rv	F	63.2	4,360	68.9	2,480	4.5	17.6	40.0

individuals (table 2) We have been unable to detect any alterations in the blood volume due to the menstrual cycle in normal women

The ability to estimate carbon monoxide in blood with an accuracy of about 0.1 volumes per cent is of advantage because it reduces the amount of gas which must be administered in order to obtain a sufficient blood concentration for satisfactory blood gas analysis. Amounts in excess of 200 cc have been used by Haldane and by Douglas, and about 150 cc by Plesch (13) and by Salvesen. We use from 90 to 110 cc for the normal adult of average weight, and proportionately less for lighter individuals. We have summarized the results obtained

TABLE 3

Comparison of average results for the blood volume obtained by various observers, using the carbon monoxide method

Author	Number of subjects	Amount of gas inhaled	Mixing time	Blood volume		Blood volume		
				Maximum	Minimum	Maximum	Minimum	Average
		cc	minutes	cc	cc	cc per kgm body weight	cc per kgm body weight	cc per kgm body weight
Haldane-Smith	12	±200	3	4,450	2,750	62.7	39.5	47.8
Douglas	2	±200	±20	5,583	4,637	79.8	71.7	
Pike's Peak expedition	4	±200	20-35	4,821	4,075	No weights given		
Plesch	8	±175	16-34	4,737	3,605	60.5	50.2	53.2
Smith et al. (14)	6	±4*	8-10	4,633	3,875	74.0	62.6	68.1
Salvesen	6	±160	10-15	4,601	3,464	69.9	52.3	59.5

* Cubic centimeters per kilogram body weight

by other observers (table 3). Haldane and Smith, and Douglas made analyses of carbon monoxide in blood with the method of carmine titration, a procedure which others have found unsatisfactory.

The methods used in the present study for the analysis of carbon monoxide in blood are so sensitive that the quantities of the gas which are inhaled and fixed in the hemoglobin in subjects who are only moderate tobacco users may introduce considerable error if not properly corrected by a preliminary control blood analysis. The blood of persons remaining indoors all day in the winter, especially in buildings heated with soft coal also may contain very appreciable amounts of carbon monoxide even if smoking is not indulged in.

Such a preliminary examination of the blood for combustible gas is therefore highly desirable and has in fact been made in most of our estimations and always where there was any reason to suppose that a contamination might exist

SOURCES OF ERROR IN THE TECHNICAL PROCEDURE

The measurement of the amount of carbon monoxide inhaled may be made with a probable error not exceeding 0.5 cc. The average amount of gas used is 100 cc., so that the greatest error is 0.5 per cent. The amount of carbon monoxide in the blood sample can be estimated with an error of about 0.1 volumes per cent. Duplicates usually agree within 0.06 volumes per cent. Since the amount measured is ordinarily between 2 and 3 volumes per cent, the maximum error is between 3.3 and 5 per cent. These errors are not likely to be additive. Consequently the maximal error in the technical procedures does not exceed 5 per cent and is probably less.

The amount of gas left in the bag and absorbing bottle is very small. It appears to have been neglected by the earlier workers (Haldane and Smith, Douglas). A somewhat elaborate procedure was worked out by Salvesen for its correction. We have preferred to standardize our technique by reducing the oxygen content of the inhaled mixture as much as possible and by reduction of the dead space of the breathing system. Numerous gas samples taken toward the end of our experiments have yielded values between 0.015 and 0.03 per cent carbon monoxide. The volume of the system (bottle, bag and tubing) is approximately 1500 cc., and to this must be added the pulmonary volume and dead space, say about 3000 cc., or in all 4500 cc. The maximum carbon monoxide gas unabsorbed therefore in our experiments is 1.35 cc. and the minimum is about 0.7 cc. If 1.0 cc. is subtracted, therefore, the maximum error should not exceed 0.33 per cent in a total carbon monoxide absorption of 100 cc. We believe attempts at closer approximation are unnecessary as well as fallacious unless the phase of respiration at the moment of taking the gas sample, and the exact lung volumes are also known. Due to mouth breathing in persons unaccustomed to a nose clip, the tidal air may well be 800 cc. or even 1000 cc., about 20 per cent or more of the volume of the total system. At first we used a small recording spirometer in order to be

able to measure the amount and phase of the respirations very accurately, but it shortly became evident that this procedure was unnecessary

DISCUSSION OF THE METHOD

The most important objections which have been raised against the use of carbon monoxide in measuring the circulating blood volume are, in the first place, the unknown loss which may occur due to diffusion from the blood into the hemoglobin of the muscle, and, in the second place, the uncertainty as to the uniformity of distribution of the gas among the blood corpuscles themselves. The latter question really resolves itself into the problem of the evenness of distribution of erythrocytes with respect to plasma throughout the circulation, for it is hardly conceivable that even distribution of the gas in the hemoglobin of the erythrocytes themselves is incomplete after twenty minutes. Unfortunately, it is not possible at the present time to give a definite answer to either criticism, but we think it is possible to define the maximum error which may thus be caused in blood volume estimations. If this source of error is kept in mind, it is clearly valid to apply the technique to studies in normal and pathological conditions.

The question of the identity and quantity of hemoglobin in muscle has occupied the attention of physiologists for many years. Gescheidtlen (15) long ago indicated that muscle hemoglobin does not exceed 5 per cent of the total blood hemoglobin, and a value of this magnitude has been commonly accepted. Whipple and his co-workers (16) now state, however, that the total muscle hemoglobin in dogs may amount to from 10 to 80 per cent of the circulating hemoglobin. They believe that "muscle hemoglobin is concerned with the rapid exchange of oxygen and carbon dioxide between the blood and contracting elements."

Without entering into a discussion of these figures, or of the technical procedures on which they are based, it is evident that an index of the amount of carbon monoxide which will diffuse into muscle from the circulating blood may be obtained by a study of the drop in carbon monoxide concentration in the blood which occurs in the transition from rest to vigorous muscular exercise. The capillary bed in

the working muscles under these conditions is increased many fold, and contains a much larger proportion of the circulating blood volume, while at the same time the blood flow is greatly augmented. Under such circumstances complete saturation of muscle hemoglobin should occur, the carbon monoxide concentration in the blood should drop, and the figure obtained for blood volume must be higher by the amount which has diffused into the muscle tissues. The increased cardiac output per minute with exercise will produce more even mixing of the cells.

For the reason just mentioned six exercise experiments on four normal subjects were performed in the following way after a period of thirty minutes of complete rest. Each subject, sitting at ease on

TABLE 4

The effect of exercise on the apparent blood volume and percentage of carbon monoxide in the blood

Date	Subject	Resting blood CO	After exercise blood CO	Percentile change in blood volume
		volumes per cent	volumes per cent	
November 16	H. C. C. (a)	2.08	1.94	+7.1
January 3	H. C. C. (b)	2.59	2.41	+7.3
November 18	G. A. H. (a)	2.52	2.46	+4.9
December 31	G. A. H. (b)	2.25	2.09	+6.6
November 22	E. H.	2.40	2.32	+1.3
November 30	G. G.	2.76	2.63	+2.6

a bicycle ergometer, inhaled a measured amount of carbon monoxide through a circulating system provided with valves and soda lime. Blood samples for carbon monoxide analysis were taken at the end of fifteen and of twenty minutes. These had the same carbon monoxide content indicating that a condition of equilibrium must have been reached. The subject, still breathing into the closed system, then exercised very vigorously with arm and leg muscles for six to ten minutes. At the end of this time a final blood sample was taken for analysis.

In three of these experiments (table 4) the change in carbon monoxide concentration after exercise was so slight as to be within the limits of error of the method, whereas in the other three, a just appre-

ciable although definite drop occurred. This may be interpreted as due to slightly more complete diffusion of the gas into the muscle hemoglobin, or, on the other hand, to the additional red blood cell mass thrown from the spleen into the circulation with exercise, which Barcroft (17) estimates may amount to about 200 cc in the normal individual, or about 4 to 5 per cent of the whole blood volume. The striking point is the extraordinarily slight change in the concentration of carbon monoxide in the blood produced by exercise.

The results offer no support to the suggestion that the carbon monoxide method gives results which are too low because of incomplete mixing in the smaller vessels containing an axial stream, and in which there is stagnant plasma in the "still spaces" at the periphery (18). With severe exercise more complete mixing should take place, but since no significant change occurs it seems clear that complete mixing must already have been accomplished.

The fact seems to be established that the effect of exercise is in fact not dilution but concentration both of erythrocytes and hemoglobin, a result which is plausibly explained if the red cell stores thrown out from the spleen and possibly from other sources is taken into consideration. The exercise experiments of Whipple and his co-workers (19), who found no change in blood volume after short exercise in dogs are in agreement with the above results. Broun (20) found no significant change in plasma volume, but an initial increase in cell volume and in "circulating blood pigment" as a result of brief exercise. With the exception of the work of Lindhard above cited, we have not found any record of previous studies of the blood volume in man during exercise.

We believe that the experiments described offer substantial evidence that the estimates of blood volume obtained with the present technique are maximal figures. They are too high by the amount of carbon monoxide which has escaped into the muscle hemoglobin. There is no doubt that the twenty minute rebreathing interval has afforded quite sufficient time for equilibrium to be reached with the muscle tissues. Nevertheless we have avoided shorter intervals because of the possibility of incomplete and uncertain mixing. Several experiments were made in attempts to estimate the minimal complete mixing time (fig. 1). It is seen that the curves rise at different rates

although a plateau indicating complete mixing is reached in all at the end of fifteen to seventeen minutes. We have no explanation to offer for the individual differences in the mixing time required and we have preferred to standardize our technique by continuing rebreathing until equilibrium is certainly established.

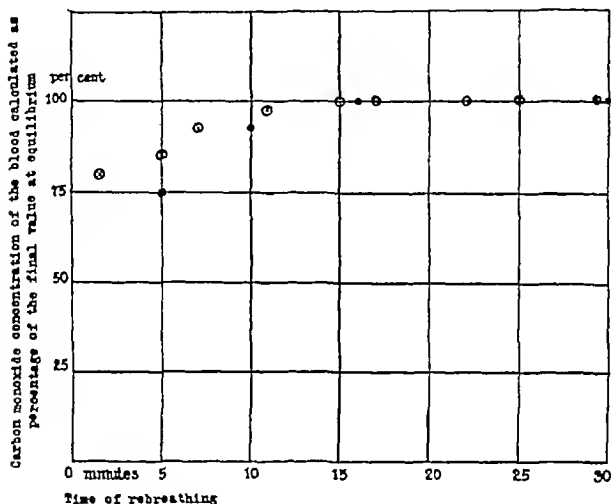


CHART 1 SHOWS THE TIME REQUIRED AFTER INTALATION COMMENCES TO SECURE COMPLETE MIXTURE

Each series of designations represents one experiment ● Experiment I
 ⊙ Experiment II ○ Experiment III

The fact that nearly all blood volume measurements in human subjects by the dye methods are from 20 to 50 per cent higher than those obtained by the carbon monoxide method, even though the latter according to the technique which we have employed must be maximal values, may be explained in large part on the grounds of insufficient mixing of the dye in the blood, as Lindhard has recently shown, in the brief interval usually allowed. The escape of the dye

into the lymph and tissue fluids, as well as the activity of phagocytes may also be factors of importance (21)

SUMMARY

1 A method for the estimation of the circulating blood volume in man is described. It consists in the inhalation of a measured amount of carbon monoxide and the subsequent estimation of its concentration in the circulating blood. The maximal error in the technical procedures involved does not exceed five per cent.

2 The circulating blood volume has been found by this method in sixteen normal individuals to lie between 60.4 and 75.5 cc per kilogram of body weight.

3 The circulating blood volume when expressed as cubic centimeters per square meter of body surface in these individuals varied between 1990 and 2860 cc.

4 The sources of error of the carbon monoxide method are discussed and the probable reasons are stated for the discrepancies in the results as compared with those of the dye methods.

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- 21 Smith H. P., *Bull J H Hosp* 1925, **xxxvi**, 325 and 1925, **xxxvii**, 177 The Fate of an Intravenously Injected Dye with Special Reference to Its Use in Blood Volume Determination Intravenous Injections of Fluid and Repeated Blood Volume Determination

THE CIRCULATING BLOOD VOLUME IN DIABETIC ACIDOSIS

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The clinical evidences of dehydration which are present during severe acidosis in diabetes mellitus raises the question as to whether alterations may occur in the volume of the circulating blood. Such alterations, if present, would influence the apparent concentration of various blood constituents in acidosis and would be of pathological significance in several particulars. It seems likely that a marked reduction in blood volume, particularly plasma volume, would have some bearing, mechanically, on the occurrence of heart failure. It may also explain in part the occurrence, frequently observed, of renal irritation and insufficiency in diabetic coma. The terminal anuria, usually ascribed to lowering of the blood pressure, may also in part be due to a similar cause. Studies of the concentration of the plasma proteins, however, or of other blood constituents (1), have not certainly demonstrated alterations in the blood concentration, and we are not aware of previous attempts to measure the actual blood volume in this condition. We have therefore undertaken a study of the circulating blood volume in diabetic acidosis and the effect of treatment upon the blood volume. The technique for the determination of blood volume described in a previous communication is especially suitable for such a study and has been used here (2).

It has appeared to us that the character of the cases studied in an investigation such as this is of great importance and that in order to ascertain as far as possible the effects of diabetic acidosis alone, other possible complicating factors must be rigidly excluded. Circulatory disorders, arteriosclerosis, renal disease, inflammation, and fever may have important effects. The number of cases presented therefore is

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small and includes only those of considerable severity in young individuals without any clinical evidences of renal or circulatory disease. The principal inciting cause of acidosis in each case chosen, so far as could be ascertained, was dietary. Cases with infection or fever have been avoided. Three of the cases had had evident symptoms of diabetes for less than six months, and had not until admission received insulin or sustained medical attention. The patient I. K. has been treated in this clinic for three years and has had known diabetes for about that period. The patient E. had been admitted to the Johns Hopkins Hospital in coma on two previous occasions. He has had diabetes for two years. No attention had been paid by any of these patients, with the exception of E., to the fluid intake before admission.

The general plan of study has been as follows. The first estimation of the blood volume was made immediately upon admission of the patient to the ward. A portion of the preliminary blood sample drawn for a control estimation of the amount of carbon monoxide present in the blood was also utilized for measuring the blood sugar and plasma bicarbonate capacity as well as the oxygen capacity, red blood cell count and cell volume. The estimation was made at once before any treatment was instituted in order not to delay unduly the prompt administration of insulin and the employment of other measures. One or more subsequent measurements were then made during or after recovery as are indicated in table 1. The later determinations were delayed until complete recovery from acute acidosis was assured and the patients appeared to be in a state of equilibrium so far as diet and insulin dosage and freedom from glycosuria were concerned. The original degree of acidosis was always well marked, as is indicated, but it was deemed unwise to attempt studies on cases of frank coma presenting definite and urgent indications for emergency treatment.

The results obtained upon the five patients studied, together with the essential clinical data were similar in each of them, differing only in degree (table 1). It will be noted that recovery from acidosis was associated in each with a distinct rise in the blood volume, which in one case increased nearly 25 per cent. At the same time there was a diminution in the oxygen capacity of the blood, in the percentage cell

volume, and, in general, a reduction in the erythrocyte count. It would seem that some relation exists between the degree of hyperpnea and the concentration of the blood, as well as the length of time during which acidosis had existed prior to treatment. The treatment consisted of the ordinary nursing measures together with the use of large doses of insulin, carbohydrates and fluids. In severe cases the fluids given amounted to as much as 8 or 10 per cent of the body weight per twenty-four hours. The fluids were given by mouth, by rectum, and subcutaneously, but in none of these patients were fluids administered intravenously. It would have been of interest to study the changes in blood volume resulting during the period of edema which is sometimes seen in poorly nourished individuals during recovery from severe diabetic toxemia, especially when the diet and particularly the carbohydrate ration is very low. None of the present cases, however, became edematous. Edema is in fact extremely rare in this clinic in the absence of manifest circulatory complications. We attribute this to the fact that care is taken to resume adequate balanced diets as early as possible, with sufficient insulin, and also to the fact that no sodium bicarbonate or other alkalies are used in the treatment.

The generalization is frequently made, and it is supported by a certain amount of evidence, that acidosis results in a loss of water from the body. In starvation this has been found to be associated with a depletion of base (3). The diuretic effect of ammonium chloride and of calcium chloride, to quote one example, is supposed to depend on the production of acidosis (4). It may be considered probable, therefore, that the blood shares in the dehydration of the other tissues during severe diabetic acidosis.

The results obtained in this study are somewhat at variance with those reported by other authors who have studied the blood volume after administration of insulin (5). The injection of insulin in animals is stated to produce a diminution of the blood volume. Its effect in human diabetes is certainly to relieve acidosis, and, as we have found, appreciably to increase the blood volume after recovery. In each of the cases reported in this paper large quantities of fluids have, however, also been given in the treatment of the acidosis and this may possibly counteract the tendency of insulin to reduce the blood

TABLE I
Circulating blood volume in diabetic patients during and after recovery from acidosis

Case	Sex	Age	Clinical condition	Total circulating blood volume cc	Blood volume		Red blood cells millions	Oxygen capacity volumes per cent	Cell volume per cent	CO ₂ capacity volumes per cent	Blood sugar mgm per 100 cc
					cc per kgm body weight	cc per sq m body surface					
E	M	24	Severe acidosis	4,980	71.7	2,660	17.8	41.0	22.0	500	
			Moderate dehydration Cooperates well Hyperpnea not marked Abrupt onset of symptoms 36 hours previous								
R E	F	19	Eleven days later Urine sugar free on maintenance diet with 30 units insulin Feels quite well No dehydration	5,230	74.5	2,830	4.6	17.6	34.5	55.0	152
			Severe acidosis Marked dehydration Marked hyperpnea. No vomiting Thirst and drowsiness for three weeks	2,980	56.5	1,760	5.3	22.2	43.3	362	
			Eleven days later Urine nearly sugar free on maintenance diet with 12 units insulin Feels much improved	3,390	75.5	2,390	5.1	19.2	40.0	183	
			Thirty-seven days later Sugar free on maintenance diet and insulin. Ready for discharge	3,570	79.0	2,510	4.3	18.9	40.0	50.0	125

D B	F	14	Moderate acidosis. Moderate dehydration. No hyperpnea. Abrupt onset of symptoms	2 250	66 0	1 760	5 2	19 9	40 0	39 0	264
			Six days later Rapid recovery on restricted diet and low dosage of insulin No dehydration. No glycosuria	2 360	69 0	1 850	4 9	17 8	39 8		184
			Twenty days later Diet and insulin dosage now well regulated. Ready for discharge	2,520	71 0	1 920	4 6	19 7	37 0	52 0	112
I K.	F	16	Moderate acidosis. Well marked dehydration. Moderate hyperpnea. Symptoms for 3 days. No vomiting	2,460	47 7	1 690	5 6	21 2	49 5	23 8	285
			Twenty three days later A very severe diabetic, responding slowly to treatment, requires 75 units insulin per day Now no glycosuria	2,890	60 0	1,953	4 5	18 2	44 0	55 1	194
T L.	M	33	Marked acidosis and desiccation. Well marked hyperpnea. Symptoms for 5 days. No vomiting Has been taking considerable fluids by mouth	4,190	68 0	2,420	5 4	21 7	48 0	18 2	326
			Thirty days later, no glycosuria on maintenance diet plus 35 units insulin. No appearance now of desiccation. Gain in weight of 4 kgm.	4,760	73 6	2,660	4 2	18 2	40 0	51 0	262

volume, if such is really its effect, in acidosis. There is other evidence, however, on the basis of changes in concentration of blood proteins which has been interpreted as indicating dilution of the blood after insulin in diabetic acidosis (6, 1). The effect of glycosuria alone in producing diuresis and dehydration has not in our experience resulted in reduction in the blood volume in diabetes.

Another factor in the production of dehydration in diabetic acidosis, and probably in the reduction in the circulating blood volume, is

TABLE 2
Changes in plasma and in cell volume during recovery from acidosis

Case	Total circulating blood volume	Plasma	Cells	Clinical condition
	cc	cc	cc	
E	4,980	2,945	2,035	During acidosis
	5,230	3,420	1,810	After recovery from acidosis
R E	2,980	1,690	1,290	During acidosis
	3,390	2,035	1,355	
	3,570	2,145	1,425	After recovery from acidosis
D B	2,250	1,350	900	During acidosis
	2,360	1,415	945	
	2,520	1,585	935	After recovery from acidosis
I K	2,460	1,245	1,215	During acidosis
	2,890	1,620	1,270	After recovery from acidosis
T L	4,190	2,180	2,010	During acidosis
	4,760	2,855	1,905	After recovery from acidosis

the loss of water which must occur from the lungs during hyperpnea. On the basis of the moisture content of air saturated at 37°, the normal adult excretes from the lungs about 500 to 1000 cc of water per twenty-four hours. During severe hyperpnea the respiratory exchange may be readily increased four to six fold with a proportionate increase in water loss through this channel. The total loss suffered in this manner, therefore, may readily amount to as much as five liters per twenty-four hours. There is every reason to suppose that in coma (cases of which we have not studied) this effect will be very

marked and that the alteration of the circulating blood volume will in consequence be very great

Table 2 gives in summary the plasma and cell volumes as calculated from hematocrit estimations. It will be noted, as was to have been expected, that the blood volume changes are chiefly due to changes in plasma volume, the volume of the cells being practically unchanged. The relationships are recorded graphically in the chart (fig 1)

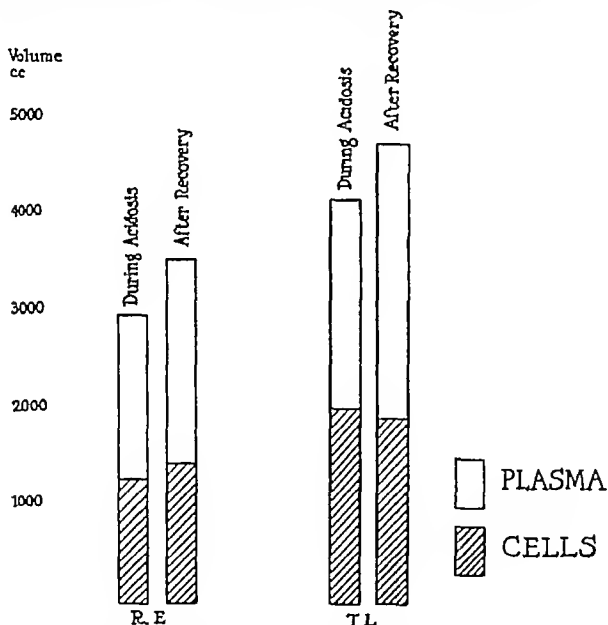


FIG 1 THE CHANGES IN THE RELATIVE PROPORTIONS OF CELL VOLUME AND PLASMA VOLUME DURING DIABETIC ACIDOSIS AND AFTER RECOVERY

SUMMARY

During diabetic acidosis unaccompanied by any other known complicating factor, a well marked diminution in the circulating blood volume was found in five individuals

This diminution was accompanied by a corresponding increase in the oxygen capacity, the cell volume, and in the erythrocyte count of the blood

The reduction in the blood volume was chiefly a reduction in plasma, the cell volume remaining intact

After complete recovery from the acidosis the blood volume increased to within the normal limits, as estimated in the preceding paper

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THE EFFECT OF HIGH PROTEIN DIETS ON THE REMAINING KIDNEY OF RATS

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In recent years much interest has attached to the rôle of high protein diets in the production of renal lesions. Newburgh (1) found varying degrees of tubular injury in rabbits fed egg white, casein or soy bean, but he describes no glomerular lesions. Squiers and Newburgh (2) found albumin and casts and red cells in the urine of hypertensive patients after feeding high protein diets. Newburgh and Clarkson (3) described dilatation of the tubules and some slight scarring of the glomeruli in rabbits after feeding 37 per cent lean beef for 6 to 12 months. In 1923 Polvogt (4) found degeneration of the tubules and some glomerular damage in rats on diets containing 31 to 41 per cent protein. Evans (5) produced both glomerular and tubular damage in rats with high protein diets but the diet was deficient in both vitamins and salts. Osborne and Mendel (5) describe tubular and glomerular lesions in high protein rats but the lesions were very slight except for a few animals over 400 days old, and furthermore similar lesions were found in animals of the same age on low protein stock diets. They do not claim to have produced nephritis.

On the other hand, Osborne (7), Drummond (8), Reeder (9), Miller (10), Jackson (11), Addis (12), and Kennedy (13) have all failed to produce significant renal lesions by feeding large amounts of protein to intact animals over a considerable period of time.

Moise and Smith (18) report their findings on 200 rats, from which one kidney was removed prior to their being put on high protein diet. The animals were 120 days old at the start of the experiment. The diet contained 85 per cent casein and was otherwise adequate for growth. The experimental period lasted from 3 to 150 days. They report that after 90 days all the animals showed significant changes

in both the glomeruli and the tubules. There was proliferation of the Bowman's capsule, serum in the capsular spaces, adhesions between the capsule and the tuft, and occasionally hyaline casts in the often dilated and degenerated tubules. They found further that the rats on normal diets excreted from 18 to 35 mgm albumin in the urine a day, while those on high protein diets excreted from 30 to 63 mgm a day. They suggest that much of the previous difference of opinions between various authors could be explained on the variable age of the animals used, as they find that the younger animals are more resistant to the toxic action of dietary protein than older ones.

In this paper we wish briefly to report the findings in a series of white rats kept on a diet containing 76 per cent casein for periods of from 2 to 17 months after the removal of one kidney. The series is admittedly small. Eighteen rats from 2 to 8 months old had one kidney removed and were then placed on adequate diets containing 76 per cent casein and described in a previous paper (11). Two rats as controls were placed after nephrectomy on standard diets containing 18 per cent casein. At intervals the various rats were placed in individual metabolism cages and their urine examined for albumin and casts. The animals' weight was periodically recorded. At the end of the experimental period they were killed, the organs were fixed in Zenker's solution and stained with eosin methylene blue. Blood was collected at the termination of the experiment and the non-protein nitrogen determined. Eleven of the rats were on a high protein diet for a year or more, yet the degree of renal damage could not be entirely satisfactorily correlated with either the age of the rat or the duration of the experiment. Rats 1, 2, 3 and 4 showed by far the most serious lesions. In all of these were found marked dilatation of the tubules throughout the kidney substance with flattening of the lining epithelium, moderate to severe fibrosis of practically all of the glomeruli with hyaline changes and occasionally vacuolization within the tuft, and scattered areas of tubular damage with subsequent cellular regeneration. In a few places hyaline deposits were found in the tubular epithelium. The glomeruli were often adherent to the capsule. Casts were present in great numbers. The glomeruli were often nearly devoid of blood cells. Pigment was found frequently in the tubules and occasionally in the interstitial tissue. Round cell

infiltration was common. On the other hand, rat 8 was on the diet longest (17 months) yet showed very few renal lesions.

The non protein nitrogen of the blood in the 18 rats on high protein varied from 40 to 160 mgm per 100 ml. In but 2, however, was it above 55 mgm—a figure often equalled and sometimes surpassed in animals with intact kidneys on a 76 per cent casein diet (11). Rats

TABLE I

Rat number	Initial age	Final age	Time on diet	Initial weight	Final weight	Weight of left kidney	Weight of right kidney	Final urine albumin	Non-protein nitrogen	Remarks
	months	months	months							
1	6	20	14	337	337	1.4	2.8	591	55	Marked renal damage
2	7	20	13	370	347	1.6	2.9	370	49	Marked renal damage
3	7	20	13	396	290	1.6	4.3	450	160	Marked renal damage
4	6	16	10	232	210	0.8	2.6	155	80	Marked renal damage
5	6	14	8	253	247	0.8	1.9	33	50	Very slight changes
6	8	23	15	379	370	1.8	3.2	40	54	
7	6	14	8	342	349	0.9	2.2	42	51	
8	8	23	17	347	427	1.0	3.3	44	46	Very slight damage
9	6	10	4	257	257	0.9	1.8	6	49	No casts
10	6	11	5	227	229	0.7	1.6	6	47	No casts
11	4	17	13	259	319	0.7	1.8	46	44	
12	5	19	14	240	241	0.9	1.8	94	43	
13	4	17	13	170	190	0.7	1.5	38	51	
14	3	16	13	252	245	0.9	1.8	150	49	No apparent damage
15	2	13	11	130	231	0.9	1.7	8	40	
16	3	15	12	169	242	0.8	2.8	124	50	
17	3	16	13	140	230	1.3	3.0	42	46	
18	6	8	2	255	240	1.1	1.2	6	40	No casts
19*	6	23	17	242	319	0.9	1.8	16	33	No casts
20*	6	23	17	255	280	1.0	1.8	16	36	No casts

* Rats on standard diet of 18 per cent casein.

5, 7, 8, 9, 14 and 16 showed very few if any renal changes. Rats 6, 10, 11, 12, 13, 15, 17 and 18 showed lesions similar to those in rats 1, 2, 3 and 4, but of very much less extent. In fact, the glomerular lesions in these former rats might well be missed on casual observation whereas the picture in numbers 1, 2, 3 and 4 was that of an advanced chronic glomerular nephritis. In none of the animals did we find the exten

sion of the renal epithelium into the capsular space mentioned by Moise and Smith

Though apparently healthy, a few of the rats lost weight. The majority showed increased urinary albumin, in one case as high as 591 mgm a day. Four rats showed no increase of urinary protein over the normal and of these three were on the experimental diet over 120 days. Nearly all animals showed casts. The average hypertrophy of the remaining kidney in the high protein group was 136 per cent. The average hypertrophy in the two standard diet rats was 100 per cent. As has been indicated, the extent of renal injury apparent at autopsy differed markedly from animal to animal. In some, the tubular damage was considerable while the glomerular damage was insignificant or wanting. In others, the lesion was mainly glomerular. In some, no lesion could be demonstrated other than an occasional dilatation of the tubules. It would seem that the tubular damage was the first to be produced and that the glomerular damage was a natural sequel or a later event. We can offer no more satisfactory explanation of these variations than age together with a varying individual susceptibility of the animals, and it is noteworthy that rats 1 to 4 inclusive came from a different stock from the rest of the animals. In general, however, we agree with Moise and Smith that age is an important factor.

The glomeruli seem to increase in size slightly above the normal but it would appear that the glomeruli also increase in size with partial nephrectomy and normal diet. The glomeruli of rats on high protein diets averaged 0.084 mm at the onset and 0.117 at the end of the experiment, an increase of 36.5 per cent. The glomeruli of rats on normal diets averaged 0.084 mm at the onset and 0.109 mm at the end of the experiment, an increase of 24.0 per cent.

That renal lesions have been produced is certain. The relation of the production of these lesions by such violently abnormal diets to the problem of human nephritis is quite another question. Severe nephritis was undoubtedly produced in four animals. In the remaining 14 the lesions were relatively insignificant yet these rats all excreted through their remaining kidney on the average 1.2 gram of nitrogen a day for about a third of their lifetime. For a healthy man of 70 kgm with two kidneys to duplicate this experiment he would have to ingest approximately 44 pounds of meat a day for 20 years.

Winter (14) reports an analysis of 237 cases of solitary kidney in man. Compensatory hypertrophy was almost always present. Of the 237 cases 171 were sound or merely enlarged. 21 had nephritis. Anders (15) found 16 cases of nephritis in 61 cases of single kidney. Manson (16) reports 3 cases of single kidney and in all 3 cases the remaining kidney was normal. Lyons (17) reports 2 cases with the remaining kidney normal. At the Boston City Hospital there have been 12 cases of congenital absence or congenital atrophy of one kidney. In 8 of these the remaining kidney was normal. In the remaining 4 there was some evidence of chronic nephritis, though in no case was the process the cause of death.

It would seem that nephritis is rather more liable to develop in single human kidneys than when both are present, and from the present work and that of Moise and Smith it would seem wise to avoid a large excess of dietary protein when one kidney is absent or markedly diseased.

CONCLUSIONS

Our experience with a small series of rats from which one kidney had been removed confirms the results of Moise and Smith in that a high dietary protein has produced at least some and often very severe damage to the remaining kidney.

We would agree with Moise and Smith that older animals are more liable to this damage but we feel that individual susceptibility is a very real factor in determining the degree of damage.

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FIG 1 RAT 2 SHOWING DILATATION OF TUBULES AND ROUND CELL INFILTRATION $\times 100$

HIGH PROTEIN DIET

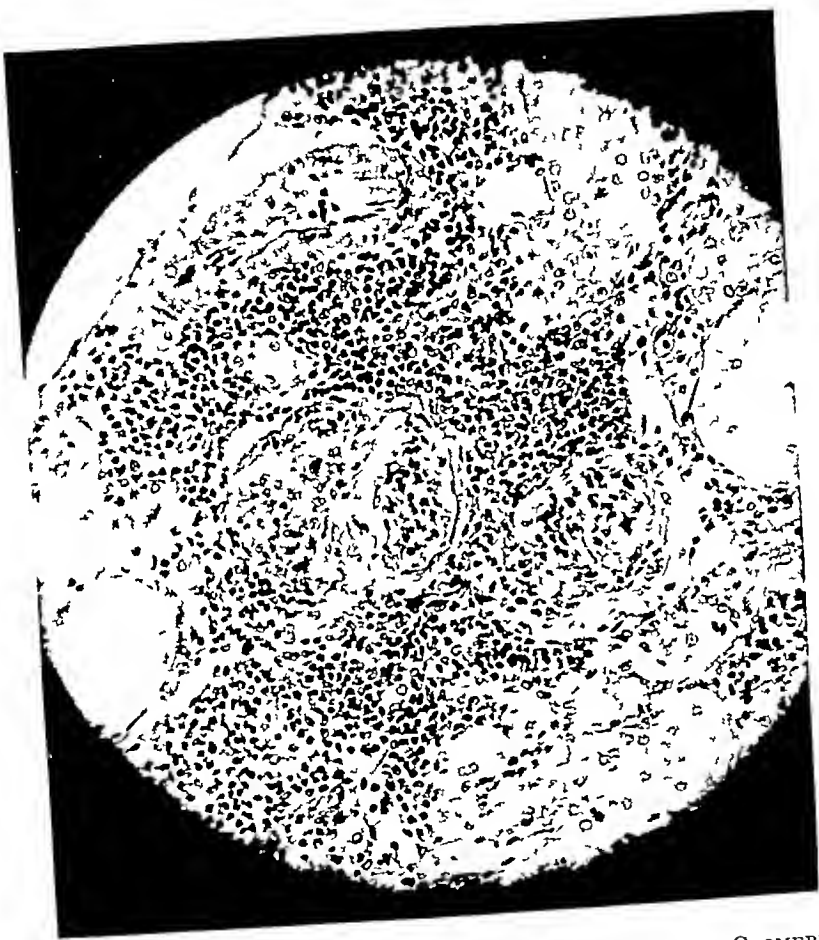


FIG 2 RAT 1 ROUND CELL INFILTRATION AND FIBROSIS OF GLOMERULI

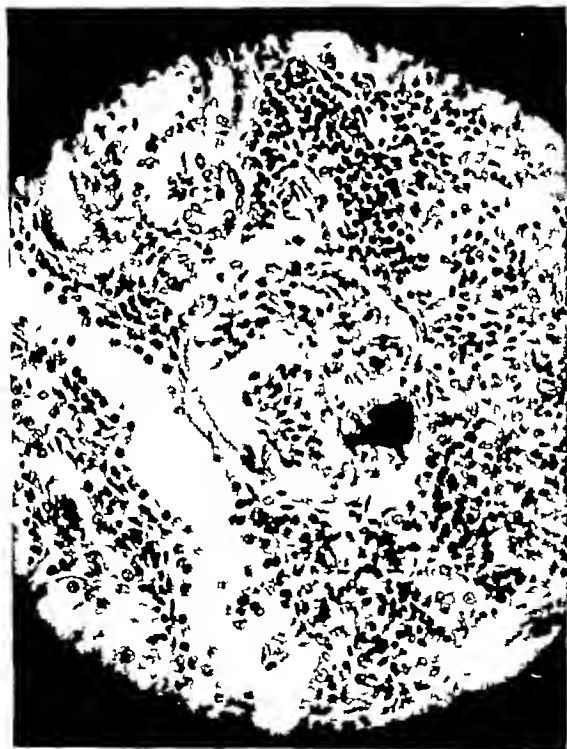


FIG 3 RAT 2 HYALINE DEPOSIT IN SCARRED GLOMERULUS $\times 320$

HIGH PROTEIN DIET

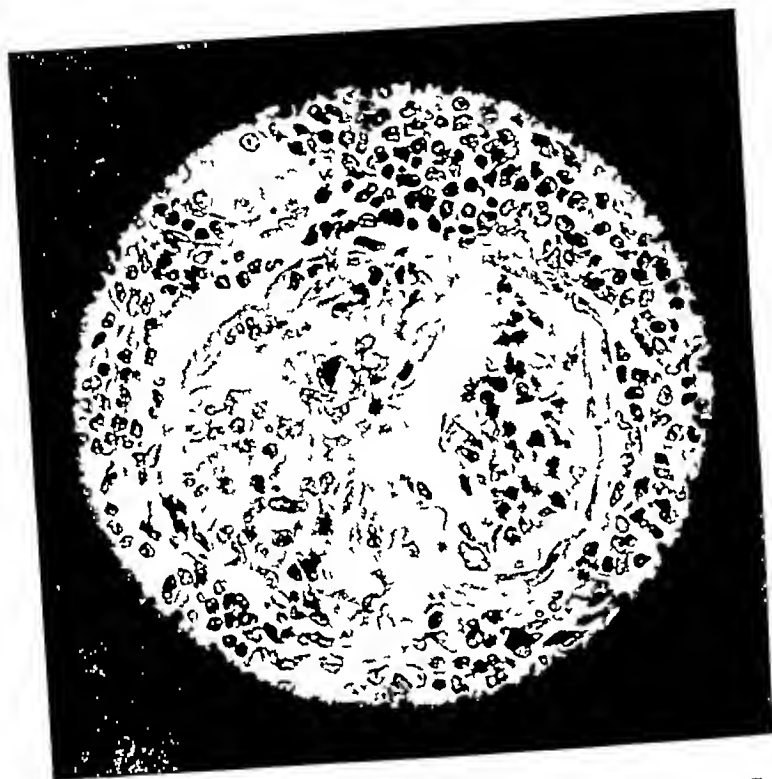


FIG 4 RAT 10 SCARRING OF GLOMERULUS WITH PROLIFERATIVE CAPSULAR
CHANGES $\times 400$



FIG 5 RAT 6 VACUOLIZATION SEEN IN MANY GLOMERULI $\times 450$

THE EFFECT OF ANTI-RHEUMATIC DRUGS ON THE ARTHRITIS AND IMMUNE BODY PRODUCTION IN SERUM DISEASE

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Serum sickness, the group of symptoms which follows the administration of foreign serum to human beings, was first extensively observed and recorded clinically by Von Pirquet and Schick (1) and later by other groups of workers. These studies concerned themselves entirely with the clinical and serological aspects of the disease, but up to the present little or no attempt has been made to obtain a method of treatment to prevent or lessen the severity of this illness. The present study was undertaken, therefore, with this in view. This work was suggested by the findings of Boots and Swift (2), who showed that in patients with serum sickness the involved joints contained a cellular exudate in which the proteins of the horse serum could be demonstrated. They also pointed out that salicylates had little effect upon the course of the illness when administered after the onset of arthritis.

During the past two years we have studied the serum-treated patients in this Hospital to determine, first the influence of the early institution of anti-rheumatic therapy upon the course of the disease, and, second the effect of such therapy upon the antigen and antibody content of their sera.

Neocinchophen, because of its anti-exudative influence in acute rheumatic fever (3) and the ease with which it is tolerated by patients, was employed in the first twenty-five cases, it was replaced by aspirin in the last nine. Depending upon the age and weight of the patient and his tolerance for the agent, neocinchophen was used in amounts of 8 to 10 grams daily, aspirin in doses of 5 to 6 grams. Drug treatment was usually begun from 24 to 48 hours after the last serum injection, and continued for 10 to 14 days. As the advantages of

early and prolonged therapeusis quickly became evident, this schedule was strictly followed with the exception of four instances in which either dosage or duration was insufficient. As identical results were obtained with both drugs, the two series have been analyzed as one group. All patients were carefully examined daily for the appearance of lymphadenopathy, urticaria and arthritis, and the signs and symptoms, whether positive or negative, were charted along with the temperature and pulse records. The degree of intensity of the respective manifestations was recorded by using the — sign, or one or more + signs, according to their severity.

As different observers have reported variations in the frequency of the individual manifestations of serum disease, we have thought it best to use as controls for this series the incidence of the various symptoms in the patients treated in this Hospital previous to the time of this study. In this way the elements of dosage of serum and type of infection—lobar pneumonia—for which it was given were constant. The records of 65 such controls were analyzed and compared with those of 34 patients subjected to anti-rheumatic therapy. In 30 of the latter, treatment was continued for a sufficient period, in 3 others its premature cessation was in each instance quickly followed by the development of arthritis. One of these is represented as the case of severe arthritis in the column marked "Treated" of table 1, in one there was moderate and in another a slight arthralgia. In a fourth patient, moderate arthritis developed because of insufficient, even though adequately prolonged, treatment.

Table 1 shows the frequency and severity of arthritis in these two groups. Of the treated patients, over 82 per cent showed little or no arthritis as compared with only 50 per cent in the untreated group. The percentages with moderately severe arthritis were about the same in each series, i e., 14.6 per cent of the treated patients and 15.2 per cent of the untreated. Further, it will be noted that only the one patient mentioned above, who was insufficiently treated, or 3 per cent of the treated patients, had a severe arthritis, compared with over 30 per cent among those untreated. Thus, as is well shown in this table, the lessening in the frequency and severity of the arthritis in the treated patients is quite evident. No comparison as to the duration of joint involvement in the two series has been attempted.

In table 2 is given the comparison of the degree and frequency of urticaria in the same two groups. Of the untreated patients, 77 per cent showed little or no urticaria as compared with 11.8 per cent of those treated, 31.9 per cent of the untreated patients showed a mild to moderate urticaria as compared with 14.7 per cent of the treated,

TABLE 1
Comparison of arthritis in treated and untreated patients

Untreated patients			Treated patients	
Degree of severity	Number	Per cent of total	Number	Per cent of total
—	27	40.9	22	64.7
±	6	9.0	6	17.7
+	5	7.6	2	5.9
++	5	7.6	3	8.7
+++	12	18.2	0	0
++++	8	12.1	1	3.0
No mention	3	4.5		
Totals	66	100 per cent	34	100 per cent

TABLE 2
Comparison of frequency and severity of urticaria in treated and untreated patients

Untreated patients			Treated patients	
Degree of severity	Number	Per cent of total	Number	Per cent of total
—	2	3.0	4	11.8
±	3	4.7	0	0
+	11	16.7	2	5.9
++	10	15.2	3	8.8
+++	24	36.4	10	29.4
++++	16	24.0	15	44.1
Totals	66	100 per cent	34	100 per cent

while 60.4 per cent of the first series showed severe urticaria as compared with 73.5 per cent of the second.

Although there was little difference in the frequency of urticaria in the two series, this symptom was more intense among the treated patients. As shown in the table, the number of patients with severe urticaria was 13 per cent less among those not receiving anti-rheumatic

drugs Whether these drugs, which are known occasionally to cause exudative dermatoses in susceptible individuals, may exert a synergic influence and thus increase the severity of the exudation into the skin of patients with serum disease, is a question we cannot answer with certainty Such an explanation is, however, not unreasonable But in spite of this statistical evidence, the great comfort resulting from the nearly complete elimination of arthritis more than counterbalances this undesirable effect

Adenopathy was present with sufficient frequency to demonstrate that the therapy was apparently without effect upon its incidence As only rarely is it a source of discomfort to the patient, it will not be further considered Febrile reactions of varying intensity were quite regularly observed How far they were influenced by the well-known antipyretic effect of the drugs employed it would be unprofitable to conjecture at the present time

As soon as it was evident that a definite anti-arthritic influence of anti-rheumatic drugs could be demonstrated in serum sickness, it became desirable to determine whether there was any parallelism between this phenomenon and the immunological manifestations of the disease

The sera of twenty treated patients were therefore studied with respect to the elimination of horse serum and the appearance of anti-horse precipitin For this purpose blood was obtained as soon as anti-rheumatic therapy was instituted, or just prior thereto, and at intervals thereafter of four to seven days during the remainder of the hospitalization In a number of instances it was possible to procure further specimens at varying intervals following discharge

Since the early studies of Hamburger and Moro (4) various observers (5) have commented upon the antigen-antibody relationships in serum disease Longcope and Rackemann (6) observed that in this condition anaphylactin and precipitin for horse serum appeared in the blood stream shortly before recovery, and that the occurrence of antibody in high titer was accompanied by rapid diminution or complete disappearance of the circulating antigen In the serum of patients who failed to develop serum sickness such antibodies were not found In their opinion the neutralization or destruction of the antigen by these antibodies was the determining factor in recovery

More recently Mackenzie and Leake (7), following a careful study of nineteen patients to whom serum had been administered, were able to distinguish three types of serological behavior. In the largest group were included those individuals who suffered from severe serum disease, and in whose sera precipitin appeared. Under these conditions the horse serum was found to disappear from the circulation near the end of the disease, at a time when the precipitin was present in high titer. In the second group were included a few patients who failed to develop serum disease, and in whose sera no precipitin could be demonstrated. In these patients the antigen persisted in the blood stream for extended periods of time. The third group was intermediate its members, although suffering from serum disease, produced antibodies only in low titer, and antigen could consistently be demonstrated in their sera, though in reduced concentration with the passage of time.

In spite of differing theoretical interpretations, there has been no dispute concerning the actual serological findings of untreated serum disease. It has therefore seemed permissible to utilize the observations of Longcope and Rackemann and of Mackenzie and Leake as controls upon the results reported in this study, especially as the amounts of unconcentrated serum administered were practically the same in the different groups.

METHODS

Anti-sera were prepared by daily subcutaneous injections into rabbits of undiluted horse serum in doses of 0.2 cc. As soon as a precipitin titer of 1:40,000 or better was obtained the animals were exsanguinated, usually one week following the final injection, and the sera were stored in the ice box without preservative. To avoid confusion from the possible presence of antigen in the blood stream at the time of bleeding each serum was titrated in ascending dilutions against each of the others. No serum was used with which any suspicion of clouthing was observed.

To test for the presence of antigen (horse serum) in the patients' sera, 0.2 cc. of a mixture of equal parts of anti-serum and normal salt solution was placed into each of a series of small tubes and the human serum to be tested was added in 0.2 cc. amounts in dilutions ranging from 1:2 to 1:200,000. All readings were expressed in terms of the final dilutions of human serum resulting. In view of the small amount of anti-human precipitin present in most high titer rabbit anti-horse sera, many control series were made with sera from healthy subjects.

In addition, as a check against deterioration of the precipitin, normal horse serum was titrated against the anti-serum employed each day that tests were carried out. The same anti-serum was always utilized for testing the entire series of bleedings from any given patient.

The same general technique was followed in testing the sera of patients for the presence of antibody (anti-horse precipitin). Into each of a series of small tubes was placed 0.2 cc. of the undiluted human serum, and normal horse serum was added in 0.2 cc. amounts in dilutions ranging from 1:2 to 1:200,000. Results were expressed in terms of the final dilutions of horse serum. A control series were always employed in which serum from a normal human subject was tested against the same dilutions of horse serum.

All tests were incubated in the water-bath at 37°C. for a period of two hours, following which they were left over night in the ice-box. Readings were made upon the following morning.

Usually the sera were tested within a few days of the bleeding. A few specimens were preserved in the ice-box for periods varying up to five weeks before being titrated. Several comparative observations revealed no significant differences in the results obtained before and after the lapse of such an interval.

RESULTS

With respect to their immunological behavior, our series of treated and serologically tested cases may easily be divided into three groups.

Of these the first corresponds with group 2 of Mackenzie and Leake, and includes those patients, four in number, in whom there was little or no evidence whatever of serum disease. The sera of these individuals failed consistently to reveal the presence of antibody, and the titer of the antigen remained at a high level throughout their stay in the hospital, showing but a slight diminution toward the time of discharge. Two of these four were observed at intervals following their discharge, in one case the antigen had disappeared from the blood stream at the end of three months, while in the other traces were still present at the end of two and a half months. Antibody was not detected at any time. Chart 1 represents a typical member of this group.

The second group, the largest of all, comprises those patients, eleven in number, in whom signs of serum disease were indubitably present, but who through adequate therapy failed to develop arthritis. Chart 2 shows a typical example of this group. Four of them failed to show precipitin during their hospitalization, while in three others

it was present during this period only in evanescent traces. In three more it was found to the extent of 1:40, while in only one instance was a titer of 1:250 reached. In only one of the seven who developed antibody did this appear in detectable amounts prior to the subsidence of the initial urticaria. The antigen (horse serum) titer in the serum remained high throughout the entire period, apparently quite uninfluenced by the development of small amounts of precipitin,

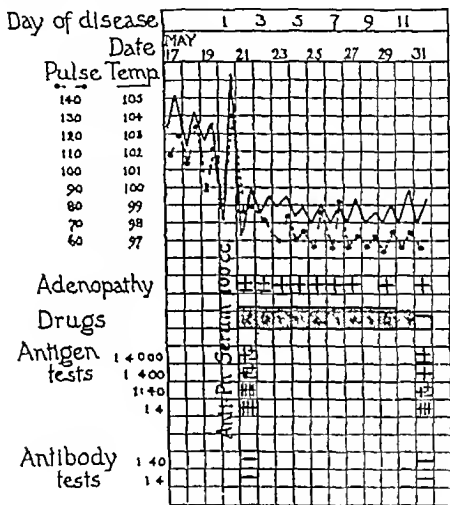


CHART 1 NO SERUM DISEASE NO ANTIBODY FORMATION
Patient received 6 gm aspirin per day over period indicated

toward the end of the hospitalization there was some diminution in the figure, but no more than was observed in the cases of the first group. Seven of these patients were observed at intervals for three months following discharge, in five instances there was complete disappearance of antigen by the end of this period, while in the sixth case only traces were found. The seventh patient still harbored demonstrable amounts of horse serum at this time, but at the end of two more

months this had vanished With a single exception, and that questionable, precipitin was never demonstrated during the follow-up period

Into the third group may be placed five patients in whom arthritis of varying degrees of severity developed

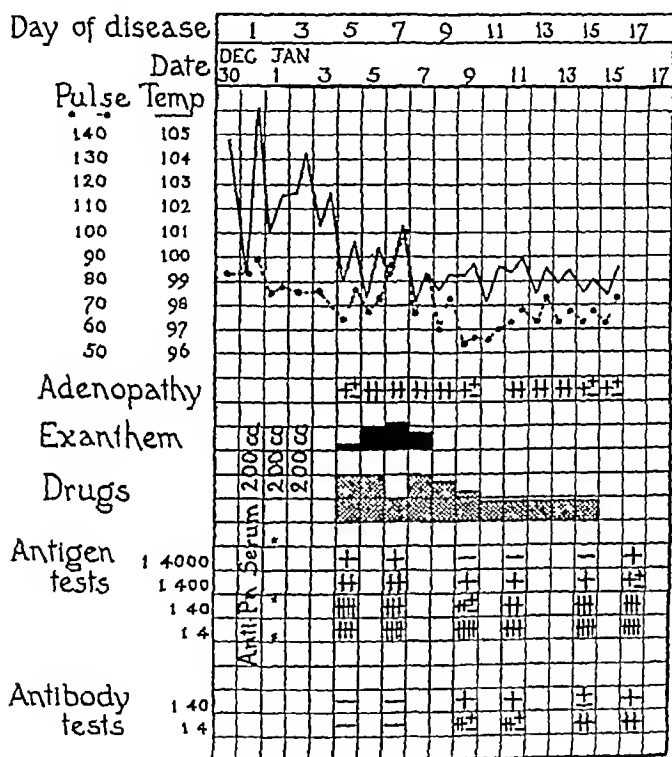


CHART 2 SERUM DISEASE, NO ARTHRITIS, LOW ANTIBODY FORMATION

Patient received neocinchophen maximum 10 gm. per day Each large block represents 5 gm

In the first case there was present on three separate days a mild arthralgia characterized principally by stiffness and vague pains, with but little resemblance to the severe arthritis of serum sickness, hence there was a reasonable doubt as to whether the symptoms should be so construed At no time was antibody present in this patient's serum and the antigen titer remained high during her hospitalization

The second patient was one in whom moderately severe arthritis developed on the twenty-fifth day following serum administration

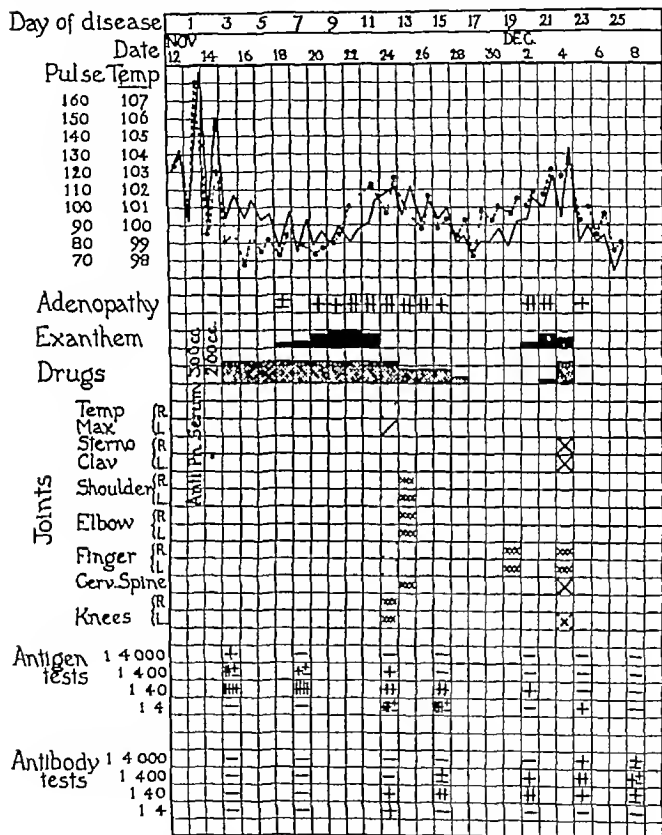


CHART 3 SERUM DISEASE MILD ARTHRITIS MODERATE ANTIBODY FORMATION

Patient received neocinchophen 6 gm. per day over period indicated. / represents pain \ represents tenderness. xxx represents stiffness.

Throughout the preceding period the antigen titer had remained high, immediately following the subsidence of the arthritis, however, a sharp drop was found to have taken place, and three weeks later only traces of horse serum could be demonstrated. At no time was it possible to detect precipitin. This was the only occasion upon which arthritis of any severity appeared in the face of adequate anti-rheumatic therapy.

The other three patients suffered moderately severe arthritis as the result of insufficient treatment. In each case antibody appeared closely upon the subsidence of the urticaria, and at the time of the arthritis had reached a titer of about 1:400. During the period of the arthritis a sharp drop took place in the antigen curve, though it

TABLE 3

Relationship between development of antibodies and appearance of arthritis

	Number of patients	Therapy		Precipitin		
		Ade-quate	Inade-quate	None	1:4 to 1:250	1:400 or higher
No serum disease	4	4		4	0	0
Serum disease without arthritis	11	11		4	7	0
Serum disease with arthritis	5	2		2*	0	0
			3	0	0	3
Totals	20	17	3	10	7	3

* Arthritis very slight in one case

never reached the base line. Following the arthritis the antibody titer remained at 1:400 and in the case of one patient, shown on chart 3, who suffered a relapse, it reached the figure of 1:4,000. Both antigen and antibody disappeared from the serum of one patient by the end of a month, and from that of a second by the end of two months. With one exception the formation of circulating antibody in titer approximating 1:400 seemed to be the necessary condition for the development of arthritis. The significance of this fact will be discussed below.

In table 3 are presented in condensed form the relationships in these drug treated patients between the existence of arthritis and the development of circulating antibody.

DISCUSSION

The foregoing observations have revealed two rather interesting phenomena. Early, adequate and sufficiently prolonged administration of aspirin or neocinchophen to patients who have received large amounts of anti-pneumococcus horse serum usually results in the prevention of one clinical manifestation of serum disease—the arthritis. Under similar therapeutic conditions there is a failure on the part of the patient to develop circulating antibodies in a concentration comparable with that shown by unmedicated controls. The conclusion seems justified, therefore, that there is some causal relationship between these two facts. It is important that the drugs be started soon after the serum treatment is discontinued, for we have frequently observed the occurrence of severe arthritis when the drugs were not given until later, even though the patients were saturated to the point of toxicity, and also when the medication was insufficiently prolonged. The clinical effect, therefore, is somewhat different from that observed in rheumatic fever, in which a severe arthritis usually disappears shortly after the exhibition of full therapeutic doses.

The observations of Boots and Swift (2) indicate that the so called arthralgia is a true inflammatory process, or at least is characterized by the presence of cellular exudate in the synovial fluid. It is interesting, further, to note that not all of the clinical manifestations of serum disease occur simultaneously, but that fever, adenopathy and urticaria usually precede the arthritis. In those rare cases in which there is a relapse of the serum disease the skin manifestations ordinarily differ from those seen in the first attack. The primary skin rash is practically always urticarial in nature, the second, if such occurs, is very finely macular or maculopapular, often situated about the hair follicles, apparently involving, therefore, some of the special organs of the skin rather than the skin as a whole. In an occasional case of the latter type which we have had the opportunity to study the precipitin titer at the time of the relapse has been distinctly higher than at the time of the first bout.

Opie (8) has shown that there is a rough parallelism between the intensity of the Arthus phenomenon and the concentration of precipitin in the sera of rabbits immunized either actively or passively to a soluble foreign protein. He concurs with the opinion, expressed

by others, that the inflammatory process is a reaction to an irritating compound which is formed by the local union of antibody and antigen. Several years ago one of us (9) showed that salicylate medication during the course of immunization partially inhibited antibody production in rabbits. The present observations seem to indicate that the two anti-rheumatic drugs used have a similar effect in human beings. If, however, all of the symptoms of serum disease were dependent upon the concentration of circulating antibodies it would be expected that drug treated patients would be practically free from any manifestation of the disease. Such is not the case, hence another explanation is required.

In recent years the view has been gaining ground that the cells of the reticulo-endothelial system play the chief rôle in the production of antibodies. Aschoff (10) and his co-workers have shown that not all of the cells of the body or even of the reticulo-endothelial system react similarly towards parenterally introduced particulate dyes or carbon particles. Certain groups of cells take up these particles readily, other groups do not react until after a more prolonged or intense exposure to the dye. Those of the skin stain very readily with trypan blue. It is probable that they absorb soluble proteins contained in foreign serum even more easily, and react by the production of antibodies. According to the theory of sessile and free antibodies a certain concentration of antibodies must be attained in the cells before they are set free into the tissue juices, and are detectable in the serum. Coordinating our observations with this theory we are led to the following explanation of the observed phenomena. The drugs so alter conditions that antibodies are discharged into the blood stream in very small amounts or not at all. This effect might follow either a lowered intracellular concentration or an altered permeability of the cell membrane. It seems, however, that antibodies must exist in the cells, for at a certain time the tissues give evidence of the presence of some irritating substance which probably results from the union in the cells of antigen and antibody, in sufficient concentration. In other words, the urticaria is an evidence of the active immunization of the reticulo-endothelial cells of the cutaneous tissue.

The fact that the arthritis in this disease appears later and practically only when there is a fairly high concentration of antibodies in the

serum, suggests that the cells of the articular tissue must be passively sensitized with antibodies before they are in a condition to show an inflammatory reaction. In other words, while the irritating substance that stimulates the inflammatory reaction may be the same in both the skin and joints, in the case of the former it is the result of active immunization of the cells, while in the latter it is the result of passive immunization. When for any reason this passive sensitization does not take place the patient remains free from arthritis. Support is given to this theory by the type of dermatitis observed in relapsing serum disease. Here, again, another type of cell seems to be involved than that taking part in the primary urticaria, and, as above mentioned, there is usually a concomitant high concentration of antibodies in the patient's serum. It is probable that the tissues of the skin involved in the relapse have been passively sensitized in the same manner as have those of the joints.

Another possibility must be considered. Dale and Hartley (11) have shown that when an animal is injected with a mixture of antigens the maximum time of immunization or sensitization may be different for each individual antigen. It is well established that serum contains several distinct antigenic proteins, and it is possible that the urticaria is attributable to a toxic antigen antibody complex involving one serum protein and the arthritis to a similar complex involving another. It is also possible that the depressing influence of the drugs on antibody formation is more powerful against the more slowly forming hypothetical arthrotropic antibody. If this were true one would expect with a complex antigen such as horse serum to demonstrate two curves or a curve with two peaks, one at the time of urticaria and another at the time of arthritis. Such a complex curve is rarely if ever found. We are, therefore, more inclined to the theory of active sensitization of the skin and passive sensitization of the joints as an explanation of the observed phenomena.

SUMMARY

- 1 If, immediately following the discontinuance of serum therapy, neocinchophen or aspirin in adequate dosage is given to patients and continued throughout the usual period of serum disease, arthritis is usually prevented even though other manifestations of serum disease occur

2 The serum of patients treated in this manner usually fails to contain anti-horse serum precipitin, and only rarely shows a precipitin concentration above 1 40

3 Usually a precipitin content of 1 400 is necessary before the patient shows arthritis

4 The theory is advanced that urticaria in serum disease is the result of active sensitization of the skin which is not prevented by the drug treatment, while the arthritis is the result of passive sensitization of the joints which is inhibited when the circulating antibodies in the serum are kept to a low concentration by the anti-rheumatic drugs

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LOW BASAL METABOLISM FOLLOWING THYROTOXICOSIS

I TEMPORARY TYPE WITHOUT MYXEDEMA, WITH SPECIAL REFERENCE TO THE RÔLE OF IODINE THERAPY¹

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INTRODUCTION

In following cases of toxic goiter for the past two years we have been much impressed by the frequency with which low basal metabolic rates occur after thyroidectomy. During this time (1925-1927), basal metabolism below minus 15 per cent was observed in at least one-quarter of the cases of toxic goiter treated in this hospital. All such cases on record since the clinic began in 1914 were then collected. A study of the resulting data revealed some striking facts, one of which was that about half of these low rates were only temporary in duration, the other half being of the type which, by way of contrast, we call permanent. The corresponding clinical pictures revealed that about 65 per cent of the patients with permanent low metabolism and 90 per cent of the patients with temporary low metabolism were for the most part apparently normal individuals, showing neither signs nor symptoms of myxedema.⁴ The remaining patients showed clinical myxedema, ranging in severity from mild to full-blown.

For the sake of convenience, this study of low metabolism following toxic goiter has been divided into three sections, viz.,

- 1 Temporary low metabolism without myxedema
- 2 Permanent low metabolism without myxedema

¹ This study was aided in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

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⁴ The term 'myxedema' is used to denote any degree of true thyroid deficiency which is clinically discernible. It is not limited to the full blown typical picture.

- 3 Myxedema
 - a Temporary type
 - b Permanent type

Sections 2 and 3 are dealt with in subsequent papers (1) (2) This paper is devoted to a study of the temporary type of low metabolism without myxedema, with special reference to the rôle that iodine therapy plays in its production

LITERATURE

The only literature we were able to find with direct reference to temporary low metabolism following treatment for goiter was in a statistical report by Jordan (3) on basal metabolic rates and their relation to end-results in thyroid disease She noted that a few cases of "benign goiter without hyperthyroidism" post-operatively showed an immediate drop in metabolism to below minus 15 per cent, but without clinical evidence of myxedema These rates invariably rose later to normal without treatment Eighteen cases or 33 per cent of a "primary hyperthyroidism series" had post-operative rates between minus 16 per cent and minus 27 per cent Five only showed clinical signs of myxedema The other thirteen cases "later had higher rates without treatment" No mention is made of whether there was coincident iodine therapy or not Jordan suggests that the phenomenon is due to "an adjustment of function" of the thyroid gland

METHOD AND MATERIAL

Basal metabolic rates were determined with the Roth-Benedict portable apparatus Aub-DuBois standards were used in the calculations

Included in this series are 27 patients with toxic goiter who showed a drop in basal metabolism following treatment to below minus 15 per cent—our actual range being minus 16 to minus 44 per cent—followed by a rise to the zone of plus or minus 10 per cent or higher The low metabolism was not accompanied by myxedema

Table 1 gives an outline of the basal metabolic and clinical histories on those of the 27 patients on whom the data is not charted

Time of onset and duration

Although the time of onset of temporary low metabolism ranged from almost immediately after treatment to several years later, it is evident from table 2 that practically all the cases appeared during the first 4 months of convalescence, about half of this number occurring within the first month

In 12 out of the 27 cases, only one low metabolism was observed, mainly due to the fact that at the time, no special interest was taken in this finding. For this reason it is difficult to make any very accurate general statement regarding duration. By calculating the time elapsing from the standard normal metabolism preceding the low rate to the one following it, it is possible, however, to state that in the great majority of instances the low metabolism did not last longer than 1 to 4 months. In a few cases the duration was somewhat longer than this. As is shown later, the length of these periods of low metabolism in many instances could be regulated at will by iodine administration.

The striking absence of myxedema

Temporary low metabolism following thyrotoxicosis, in general, is not associated with clinical evidence of myxedema. Out of 30 cases collected to date, 26 never had myxedema at any time. One (case 27, fig. 4) had signs and symptoms suggestive of mild myxedema coincident with her first period of temporary low metabolism but no such signs or symptoms with three subsequent periods of temporary low metabolism. These 27 cases provide the material for this article. The 3 others, dealt with in the article on myxedema following thyrotoxicosis (2), had signs and symptoms suggestive of mild thyroid deficiency coincident with their period of temporary low metabolism, but later were symptom-free, although they again developed a low metabolism which as yet has not proved to be of the temporary type.

Given a low metabolism and that alone, one can not predict therefrom what the clinical picture will be with respect to the presence or absence of myxedema. Many of the patients in this series had as low a metabolism temporarily as is found in full-blown myxedema. For example, cases 1 (fig. 1), 2, 3, 4 (fig. 6), 5, 6, 7 (fig. 5), 8 and 27

TABLE 1
Twenty seven cases showing temporary low metabolism without myxedema following thyrotoxicosis

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
1	Mrs F A (see fig 1)		per cent		kgm	o	
2	Toxic adenoma Mrs H C Age 38 Lab No 2678	July 3, 1924 July 8, 1924 July 18, 1924 July 28, 1924 October 22, 1924 December 31, 1924 January 7, 1925 January 15, 1925 January 16, 1926	+30 +36 +12 -3 -38 -29 +11 -11	88 96 72 58 64 56 60 65	70 0 70 0 68 0 72 0 71 4 71 8 69 9 69 7	Right hemithyroidectomy	Thyrotoxicosis for 3 months Goiter + No eye signs Tremor + Palpitation Well No thyrotoxicosis Well No myxedema Well No myxedema Well No change
3	Exophthalmic goiter Miss B H. Age 18 Lab No 3287	June 5, 1925 June 7, 1925 June 12, 1925 June 14, 1925 June 20, 1925 June 22, 1925 July 15, 1925 August 18, 1925	+84 +18 -1 +3 -33	142 102 92 96 98	53 0 51 4 50 0 57 5 59 9	Lugol's solution, M XLV daily <i>Subtotal thyroidectomy</i> Lugol's decreased to M XV daily Lugol's omitted. Started NaI (saturated solution) M XV daily every other week NaI decreased to M V daily every other week	Moderate thyrotoxicosis for 9 months Goiter + Exophthalmos + Tremor ++ Much improved No myxedema "Better than ever before"

		September 16 1925	+5	94	60 2	NaI omitted	Well ? Slight residual thyro- toxicosis
4	Mr J W (see fig. 6)	November 17, 1925	+17	96	60 6		
		April 29, 1926	+12	88	57 7		
		November 5 1926	+9	136	55 7		
5	Exophthalmic goiter	October 8 1925	+37		49 7		Moderate thyrotoxicosis for 3 months. Exophthalmos ++
		October 9 1925	+44	108	48 8	Lugol's solution M VOA daily	Goiter + Tremor + Slight weight loss
	Miss B B	October 11 1925	+14	93	49 4	<i>Subtotal thyroidectomy</i>	
	Age 18	October 13, 1925				Lugol's omitted	
	Lab No 3543	October 22, 1925				Lugol's M. VIII daily	
		October 23, 1925					
		November 5, 1925	-9	80	49 7		No thyrotoxicosis
		December 7 1925	-17	70	53 9		No myxedema
		January 6, 1926	-25	76	56 9	Lugol's omitted	
		January 14 1926	-13	80	56 6		
		January 28, 1926	-3	78	54 7	Lugol's M VIII daily	
		February 11, 1926	-10	77	55 6	Thyroid extract (Armour's) grains IV as daily	
		February 19, 1926	-5	84	54 8	Thyroid increased to grains VI daily	
		February 26 1926	+5	84	53 2	Lugol's increased to M. XV daily	
		March 8, 1926	+3	88	51 7	Thyroid decreased to grains IV as daily	Much improved
		March 19, 1926	±0	87	51 4	Thyroid decreased to grains III	
		March 29, 1926	+3	82	51 2	daily	
		April 13 1926	±0	77	52 0	Thyroid decreased to grains I as daily	
		April 24, 1926	-2	68	51 5		

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes	
5	Exophthalmic goiter Miss B B Age 18 Lab No 3543	May 22, 1926	-5	71	49.5	Thyroid omitted Lugol's continued Lugol's omitted	Well No myxedema	
		June 10, 1926	-15	66	49.5			
		June 24, 1926	-12	71	49.5			
		August 26, 1926						
		December 10, 1926	+14	84	50.4		? Mild residual thyrotoxicosis	
6	Exophthalmic goiter Miss R. H Age 13 Lab No 2803	September 24, 1924	+19	120	42.0	Complete rest in bed Lugol's solution M X daily Lugol's decreased to M V daily Bed 15 hours daily	Mild thyrotoxicosis nearly 1 year	
		October 4, 1924	±0	102	42.2			Goiter + Tremor + Ex-
		November 6, 1924	+30	140	43.0			ophthalmos + No weight loss
		November 13, 1924	+9	124	44.5			Improved
		November 20, 1924	-4	112	45.0			
		December 4, 1924	-5	120			Bed 14 hours daily	Much improved
		January 6, 1925	+18	118	46.6			
		February 6, 1925	+28	114	48.4			
		March 6, 1925	+35	129	46.3		<i>First x-ray treatment</i>	Had not been resting Thyro-
		March 11, 1925						toxicosis increased
		April 2, 1925	+37	124	46.1			
		April 16, 1925					Lugol's increased to M X daily	
		May 2, 1925	+16	110	46.8			
		June 2, 1925	+1	106	48.5			<i>Second x-ray treatment</i>
					Lugol's decreased to M V daily	Thyrotoxicosis not so marked		

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
8	Exophthalmic goiter	May 12, 1927	—16	80	76 0	Lugol's omitted	Very tired
		June 10, 1927	—7	84	76 4		Tiredness gone* Perfectly well
		June 13, 1927	—6	84	76 4		No myxedema No thyrotoxicosis
		July 8, 1927	—13	70	74 9		No change
	Miss G MacG Age 20 Lab No 4155	July 21, 1927	—14	70	74 8		
		August 8, 1927	—8	65	74 8		
		August 19, 1927	—6	69	74 3		
9	Mr J D (see fig 3)						
10	Exophthalmic goiter	February 20, 1925	+59	120	49 2	Lugol's solution M XV daily	Mild thyrotoxicosis for 6 months
		February 25, 1925	+56	112	48 5		Goiter + Tremor ++ No eye signs
		March 7, 1925	+72	126	48 1		Palpitation
		March 10, 1925					
	Miss H O'B Age 18 Lab No 3061	March 16, 1925	+10	76	46 4	Subtotal thyroidectomy Lugol's increased to M LXV daily Lugol's decreased to M XXX daily Lugol's decreased to M XV daily Lugol's omitted. Started NaI (saturated solution) M V daily, alternate weeks	Much improved No myxedema
		March 18, 1925					No thyrotoxicosis
		March 19, 1925					
		March 26, 1925					
		March 30, 1925	—20	52	46 7		Well
		April 30, 1925	—2	64	52 2		
		June 1, 1925	—8	74	53 0		
		August 25, 1925	+6	88	52 2		

11	Exophthalmic goiter Miss A. S. Age 17 Lab No 4392	December 11, 1926 December 17, 1926 December 21, 1926 December 29, 1926 January 26 1927 April 1, 1927 July 2 1927	+42 +13 -1 -20 +1 +2	136 88 92 76 80 76	58 1 57 3 56 2 60 5 53 7 58 0	Lugol's solution M XV daily <i>Subtotal thyroidectomy</i> Lugol's omitted. Started KI M V daily Changed to Lugol's M. V daily Lugol's omitted	Thyrototoxic for 6 months. Goiter + Slight exophthal- mos. Tremor No myxedema. Well Perfectly well. No thyrototoxicosis
12	Exophthalmic goiter Miss V W Age 39 Lab No 2202	October 12 1923 October 15, 1923 October 20 1923 October 22, 1923 October 30, 1923 August 7, 1924 December 22, 1924 August, 1925 November 13, 1926 December 12, 1926	+30 +8 +5 +6 +3 -18	100 104 88 84 80 76	55 0 54 0 54 0 55 0 56 0 56 0	Lugol's solution M. V daily <i>Subtotal thyroidectomy</i> Lugol's omitted NaI (saturated solution) M II daily NaI decreased to M I every other day NaI omitted Lugol's solution M. V daily	Moderate thyrototoxicosis 6 to 8 months. Goiter + Tremor ++ Exophthalmos ++ Lost 6 pounds in 8 months No evident thyrototoxicosis No myxedema
13	Exophthalmic goiter Miss A. B Age 39 Lab No 4666	April 6 1927 April 7, 1927 April 18, 1927 April 21, 1927 April 25, 1927 April 30, 1927 June 1, 1927 June 23 1927 July 7 1927 July 26 1927	+33 +5 -9 -20 -9 ±0 -15	112 84 76 84 84 71 68	47 5 46 3 45 5 49 0 50 3 50 7 51 5	Lugol's solution M XV daily <i>Subtotal thyroidectomy</i> Lugol's increased to M. Lx daily Lugol's decreased to M. XXX daily Lugol's omitted. Started KI (saturated solution) M XV daily KI omitted Lugol's M. V daily	Mild thyrototoxicosis for 2 years Small goiter Exophthalmos + Tremor + Loss of 10 pounds Much improved. No thyrototoxicosis. No myxedema No change Well Well. No myxedema

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
			per cent		kgm		
14	Mr A F (see fig 2)						
15	Miss F K. (see fig 7)						
16	Exophthalmic goiter	July 25, 1924	+42	100	43 0		Severe thyrotoxicosis 1½ years
		July 30, 1924	+24	92	43 0		Goiter + Exophthalmos ++
		August 20, 1924					Tremor + Lost 40 pounds in 1 year
	Mrs M M	September 10, 1924	+54	112	42 0	First x-ray treatment	Improved
	Age 26	October 1, 1924	+45	98	43 0	Second x-ray treatment	
	Lab No 2711	October 22, 1924	+41	96	45 5	Third x-ray treatment	
						Lugol's solution M IX daily	
		November 3, 1924	+38	97	48 0		Still moderate thyrotoxicosis
		November 26, 1924				Lugol's increased to M XV daily	
		December 6, 1924				Subtotal thyroidectomy	
		December 12, 1924				Lugol's omitted	
		January 15, 1925	-12	74	51 5		Much improved
		January 23, 1925	-4	66	53 1		No thyrotoxicosis
		February 24, 1925	-19	72	55 9		
		April 1, 1925	-18	68	53 6		No thyrotoxicosis. No myxedema
		April 6, 1925				Tonsillectomy	Bed for 3 weeks with fever and joint pains
		May 1, 1925					

17	Exophthalmic goiter Mr H. E. Age 34 Lab No 3906	May 5 1925	-2	66	48	3	Cholecystectomy	Looked worn and tired. No thyrotoxicosis. No myxedema
		June 5, 1925	-10	67	48	3		No thyrotoxicosis
		July 31, 1925	-9	68	46	7		No myxedema
		October 5, 1925	-4	62	46	1		
		March 25, 1926	-6	78	47	9		Six months pregnant. Well
		April 30, 1926					Lugol's M. V daily	No myxedema. Respiratory infection. ? Tuberculous
		August 20, 1926						No myxedema. No complaints
		January 5, 1927	-18	66	46	4		Well. Slightly nervous
		February 14, 1927	-15	66	46	0		Moderate thyrotoxicosis for 1 year
		April 21, 1927	-9	72	45	0		Goiter + Exophthalmos ++
		May 24 1927	-13	68	44	0	Lugol's solution M. XXX daily	Tremor + Lost 22 pounds in 1 year
		July 25, 1927	-8	66	42	9		
		April 7, 1926	+48	120	56	5		
		April 10, 1926	+42	116	55	6		
		April 17, 1926	+47	102	54	9		
		April 20, 1926					Subtotal thyroidectomy	
		April 23, 1926	+19	92	54	4		
		April 29, 1926						
		May 15, 1926	-14	56	54	4		
		May 19, 1926						
		May 20, 1926	-18	72	52	3	Lugol's decreased to M. V daily	No myxedema. Well
		June 12, 1926	-5	80	57	1		Well
		September 10, 1926						
		September 17, 1926	-5	83	59	4		
		November 8, 1926	+11	84	62	3		Recovering from an attack of catarrhal jaundice. No thyrotoxicosis
		December 29, 1926	+8	80	62	0	Thyroid extract grains 1ss daily Thyroid omitted	Well
		February 12, 1927	+7	84	61	7		
		February 19 1927						
		April 23 1927	+19	84	61	6		
		July 23, 1927	+8	74	61	9		Well. Thought he felt better when on iodine

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
			per cent		kgm		
18	Miss L. B., age 23 (see fig 6 in study II (1))						
19	Exophthalmic goiter	August 10, 1925	+47	107	47.8	Lugol's solution M XXX daily	Thyrotoxicosis for 1 month
		August 11, 1925					Goiter + Tremor + No exophthalmos
		August 13, 1925	+24	106	48.4		Lost 12 pounds in 3 weeks
	Mrs B. P.	August 19, 1925	+6	92	49.2		
	Age 17	August 22, 1925				<i>Subtotal thyroidectomy</i>	
	Lab No 3425	September 2, 1925	-17	66	47.9	Lugol's omitted NaI (saturated solution) M V every other day	No myxedema
		November 20, 1925	+17	80	56.5		Much improved
		February 27, 1926	+14	98	54.6		
		April 17, 1926	+30	88	56.4		? Mild residual thyrotoxicosis
20	Exophthalmic goiter	May 11, 1925	+58	108	50.7		Moderate thyrotoxicosis for 6 years.
		May 20, 1925	+41	98	48.1		Goiter ++ Exophthalmos
		May 21, 1925					++ Tremor ++ Lost 20 pounds in 2 years
	Mrs. D. T.	May 27, 1925	+7	70	48.8	Lugol's solution M XV daily	
	Age 32	May 29, 1925				<i>Subtotal thyroidectomy</i>	
	Lab No 3235	June 12, 1925	-17	59	48.7		No myxedema Excellent condition
		June 18, 1925	-6	80	51.0		
		July 29, 1925	-3	70	52.3		
		September 17, 1925	+6	61	51.0		No thyrotoxicosis. Marked mental depression

21	Exophthalmic goiter Miss F DeV Age 18 Lab No 2001	May 19 1923 May 20, 1923 April 7 1924 April 9, 1924 April 30, 1924 May 20 1924 May 21 1924 May 21 1924 June 10, 1924 July 1, 1924 July 17 1924 November 20 1926	+22 +26 +29 +24 +39 +8 -16 ±0	110 117 92 90 100 74 70 76	52 52 50 0 49 50 53 49	First x-ray treatment Second x-ray treatment Third x-ray treatment Fourth x-ray treatment Fifth x-ray treatment	Mild thyrotoxicosis at least 1 year Slight exophthalmos. Goiter + Tremor + Lost 6 pounds in 3 weeks No improvement Same Improved No myxedema Perfectly well. No residual thyro- toxicosis
22	Exophthalmic goiter Mrs. D N Age 41 Lab. No 3664	November 28, 1925 December 2, 1925 December 9 1925 December 20, 1925 December 21 1925 January 11, 1926 May 19 1926 June 23 1926 September 16, 1926 October 15, 1926 January 20 1927	+37 +45 +12 +19 -16 +13 +1 +1 +2 +20	84 108 104 84 86 84 84 80 76 96	52 52 52 55 56 60 63 62 62 63	Lugol's solution M XXX daily Subtotal thyroidectomy Lugol's omitted KI (saturated solution) M XV daily	Thyrotoxicosis about 1 year Goiter Eyes stary Lost 33 pounds in 1 year No myxedema No thyrotoxicosis No definite thyrotoxicosis
23	Toxic adenoma Mrs. S K. Age 58 Lab. No 4079	July 3 1926 July 17, 1926 July 20, 1926 July 22, 1926 July 26 1926 July 31, 1926 August 3, 1926	+67 +61 +25 +41 +42	108 102 94 92 92	64 64 62 62 62 61	Lugol's solution M XLV daily Right hemithyroidectomy Lugol's omitted	Moderate thyrotoxicosis for 3 years. Goiter + Tremor ++ Nervousness. Asthma

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
23	Toxic adenoma	August 5, 1926	for cm ² +15	66	60 7	Potassium iodide (saturated solution) M V daily Lugol's M V daily	No myxedema
		August 10, 1926	-16	60	61 5		? C N S lues
		August 13, 1926					No thyrotoxicosis
		September 15, 1926	+4	76	66 9		Well No thyrotoxicosis
		June 15, 1927	+4	76	79 8		
24	Exophthalmic goiter	January 18, 1924	+24	82	46 0	Lugol's solution M XV daily	Mild thyrotoxicosis Goiter
		February 1, 1924	+27	108	45 0		Slight exophthalmos. Slight tremor Diarrhea Nervousness
							Symptoms slightly increased
							Improved
		February 21, 1924	+41	100	44 5		
		March 6, 1924	+43	90	44 0		
		March 19, 1924	+22	74	44 0		
		March 28, 1924	+20				
		May 21, 1924	-16	66	48 5		Much improved. No myxedema
		June 16, 1927	+16	78	48 5		? Mild residual thyrotoxicosis
25	Exophthalmic goiter	July 11, 1927	+36	104	47 8	Lugol's omitted	Mild thyrotoxicosis
		March 31, 1927	+55	128	59 8		Thyrotoxicosis for 1 year Severe
		April 2, 1927					at time of entry Goiter +
		April 11, 1927	+19	82	59 1		Very slight exophthalmos.
		April 14, 1927	+7	80	59 4		Tremor ++ Loss of 30 pounds
	Miss R E Age 18 Lab No 4645	April 15, 1927				Stribitol thyroidectomy Lugol's increased to M LX daily	

26	Exophthalmic goiter Mrs. M F F Age 41 Lab No 4539	<p>July 13, 1927 July 18, 1927 July 28, 1927 August 5, 1927 August 12, 1927 August 18, 1927 October 6, 1927 October 10, 1927 October 20, 1927 October 27, 1927 November 11, 1927 December 8, 1927 January 5, 1928 February 13, 1928</p> <p>February 23, 1927 March 7, 1927 March 8, 1927</p> <p>March 10, 1927 March 14, 1927 April 13, 1927</p> <p>June 9, 1927 July 7, 1927 August 5, 1927 August 13, 1927 August 20, 1927 October 6, 1927 November 8, 1927</p>	<p>-19 -17 -20 -12 -8 -14 0 -1 -6 -13 -3 +8 -13 -13</p> <p>+69 +45</p> <p>+18 +3</p> <p>-16 -11 -5 -11 -19 -23 -11</p>	<p>64 56 55 61 60 55 72 67 68 62 72 74 55 66</p> <p>72 72 72 72 72 72 71 71 73 72 72 71 73 71</p> <p>51 49</p> <p>48 57</p> <p>66 71 71 73 74 75 77 68</p>	<p>Lugol's omltted</p> <p>Lugol's M I daily Lugol's omltted Lugol's M $\frac{1}{2}$ daily</p> <p>Lugol's solution M XXX daily <i>Subtotal thyroidectomy</i> Lugol's increased to M. LX daily Lugol's decreased to M XXX daily Lugol's omltted Lugol's M V daily</p> <p>Lugol's omltted Lugol's M. V daily</p> <p>Lugol's omltted</p>	<p>Well. No myxedema No myxedema</p> <p>Perfectly well. No change</p> <p>Clinically normal</p> <p>No thyrotoxicosis</p> <p>Perfectly well. No myxedema</p> <p>Thyrotoxicosis for 1 year Severe on entry Goiter ++ Lx ophthalmos + Tremor ++ Loss of 50 pounds</p> <p>Much improved. Still very slight thyrotoxicosis Much better No myxedema Well. No myxedema No change. Well</p> <p>Well. No myxedema</p>
27	Mrs. V P (see fig 4)					

(fig 4) had rates of minus 44, 38, 33, 25, 25, 24, 23, 21 and 21 per cent respectively, yet they showed no evidence of thyroid under-function

Case 7 (fig 5) illustrates well the typical clinical picture present at the time of the low metabolism. When her metabolism was low (minus

TABLE 2
Time of onset and duration of temporary low metabolism without myxedema

Number of cases	Time of onset	Duration
10	Within 1 month after treatment	1 to 3 months in 8 cases Not accurately known in 2 cases
13	From 1 to 4 months after treatment	1 to 3 months in 7 cases 4 to 6 months maximum in 4 cases Not accurately known in 2 cases
2	From 4 months to 1 year after treatment	Not accurately known
2	Over 1 year after treatment	4 months maximum in 1 case Not accurately known in 1 case

TABLE 3
Relation between type of toxic goiter, type of treatment employed for thyrotoxicosis, and temporary low metabolism without myxedema

	Iodine only	Subtotal thyroid ectomy	Hemi thyroid ectomy	X ray, then subtotal thyroid ectomy	X ray	
		On iodine	Not on iodine	Not on iodine	On iodine	Not on iodine
Number of cases of exophthalmic goiter	2	17		2	2	2
Number of cases of toxic adenoma			2			

14 to minus 23 per cent) she had no signs or symptoms of myxedema. There was no edema. Her hair and skin were not dry. She was sensitive to cold, but had been so before she developed thyrotoxicosis. She was strong and energetic and not slowed up in any way. She could do her own housework, cooking and washing, and care for two

children without fatigue. In fact, she was exceptionally well and felt less nervous than when her metabolism was standard normal.

In case 1 (fig 1) where the metabolism fell to the low level of minus 44 per cent, the absence of clinical evidence of myxedema apparently astonished the observers, as a note in the record states "Very hard to understand."

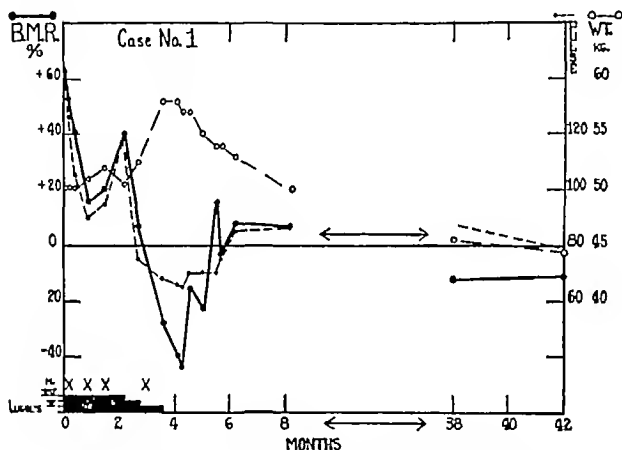


FIG 1 MRS F A, AGE 19 LAB No 2160 TEMPORARY LOW METABOLIC RATE FOLLOWING X RAY TREATMENT (X) AND IODINE THERAPY, FOR EXOPHTHALMIC GOITER

No myxedema despite the low level of the metabolism (In this and subsequent figures, black areas denote Lugol's therapy)

Influence of type of treatment employed for thyrotoxicosis, with special reference to iodine therapy

As shown in table 3, temporary low metabolism occurs after treatment of thyrotoxicosis by x ray, by subtotal thyroidectomy, or even by hemithyroidectomy alone.

A few cases had no iodine at or near the time of the low metabolic rate (see fig 2 and fig 6 in study II (1)), but in the great majority of

instances the patients were on iodine during this period. A fact worth stressing is that temporary low metabolism may occur after treatment by iodine alone, when there has been no destruction of thyroid gland tissue (see fig 7)

It is very important to know just what relation iodine therapy bears to these temporary low metabolic rates, for nearly all exophthalmic goiter patients (who constitute the great majority of our series) of

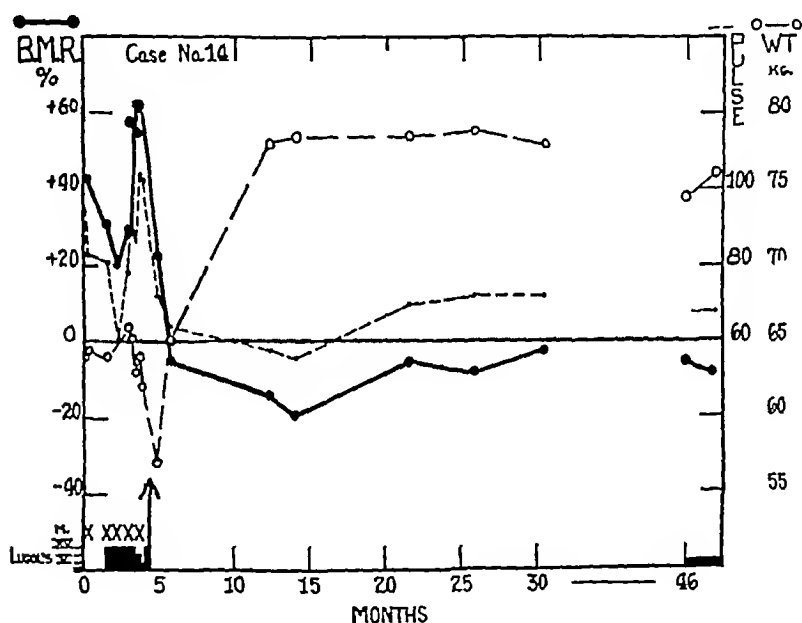


FIG 2 MR. A F, AGE 39 LAB No 2112 TEMPORARY LOW METABOLISM OCCURRING WITHOUT IODINE THERAPY EIGHT MONTHS AFTER X-RAY TREATMENT (X) AND SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

No myxedema

late years have been put on iodine preoperatively for the express purpose of lowering the metabolism, and this therapy is usually continued for a considerable time after operation, when the influence of thyrotoxicosis has been markedly reduced by surgery

In an effort to throw some light upon the rôle this medication may play in the production of temporary low metabolism, patients are classified relative to their iodine therapy as shown on following page

- 1 *Not on iodine at or near time of low metabolism* The subsequent rise to normal metabolism also occurred without medication. Cases 2, 14 (fig 2), 16, 18 (fig 6, study II (1)) and 21. See table 1
- 2 *Not on iodine at time of lowest metabolism, but iodine omitted so shortly before that it may be a complicating factor* The subsequent rise to normal metabolism occurred without medication. Cases 1 (fig 1), 6 and 23. See table 1
- 3 *On iodine at time of low metabolism*
 - a) The subsequent rise to normal metabolism occurred while still on iodine. Cases 3, 4 (fig 6), 10, 11, 17, 19 and 20. See table 1
 - b) The subsequent rise to normal metabolism occurred on omission of iodine. Cases 5, 7 (fig 5), 8, 9 (fig 3), 12, 13, 15 (fig 7), 22, 24, 25, 26 and 27 (fig 4). See table 1

In cases 12 and 13 the metabolism fell to a low level again when iodine was resumed.

Cases 5, 8, 9 (fig 3) and 26 repeated the cycle of fall and rise coincident with the administration and omission of iodine, for the second time. Cases 7 (fig 5) and 25 repeated it for the second time and their metabolism fell to a low level again for a third time on iodine. Case 27 (fig 4) repeated the cycle for the fourth time.

Referring to the above summary of the relationship between temporary low metabolism and iodine therapy, it may be seen that there were 5 cases in which iodine could have played no part in the production of the low rate and there were 3 cases where the length of time after omission of iodine made its influence somewhat open to question. But there were 19 cases in which the metabolism altered during the period of iodine therapy.

Cases 4 (fig 6), 7 (fig 5), 9 (fig 3), 15 (fig 7), 24, 25, 26 and 27 (fig 4) are worthy of special mention in connection with the effect of iodine therapy.

Cases 7, 9 and 27 (figs 5, 3, and 4 respectively) and cases 25 and 26 (table 1) illustrate particularly well the repeated depression of metabolism to a low level followed by a rise to standard normal, produced by the administration and omission of iodine. In cases 7, 9 and 27, coincident with the fall in metabolism from standard normal to a low level, nervousness and irritability decreased, the pulse became slower and the weight sometimes increased slightly. They were apparently normal individuals when their metabolism was low, and showed no signs or symptoms of myxedema. Cases 25 and 26, how-

ever, showed no clinical change coincident with the fall in metabolism from standard normal to a subnormal level, except that in case 25 the pulse became slower. At both levels they appeared to be well.

Case 4 (fig 6) is of especial interest in that $3\frac{1}{2}$ years after operation for exophthalmic goiter he showed definite residual thyrotoxicosis with

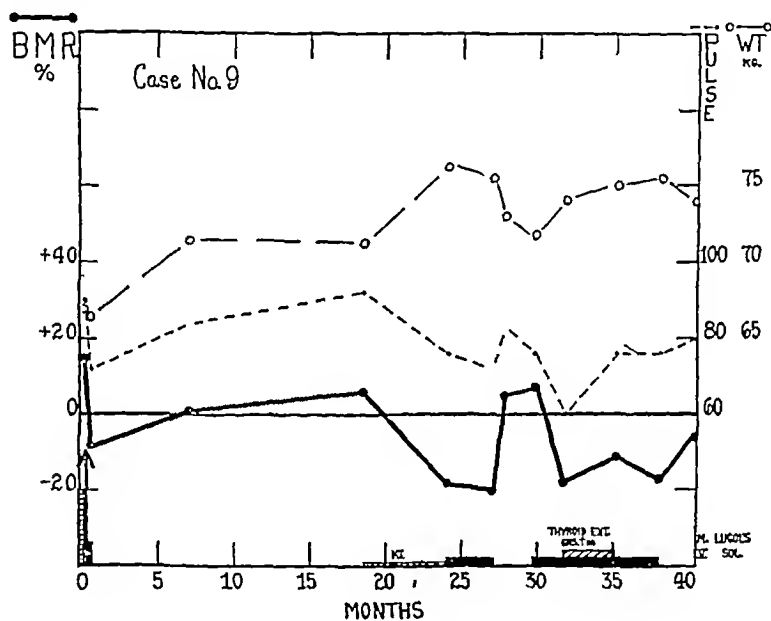


FIG 3 Mr J D, AGE 53 LAB No 2750 PRODUCTION OF A TEMPORARY LOW METABOLISM COINCIDENT WITH THE ADMINISTRATION AND OMISSION OF IODINE, $1\frac{1}{2}$ TO $3\frac{1}{2}$ YEARS AFTER SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

Relatively low metabolism before operation probably due to KI therapy. Reduction of metabolism to a subnormal level accompanied by decrease of nervousness and irritability. No myxedema although low metabolism lasted many months. Thyroid therapy produced no clinical change (In this and subsequent figures, cross-hatched areas denote thyroid therapy.)

a metabolism of only plus 4 per cent. He had tremor, exophthalmos, palpitation, increased perspiration, increased appetite and thirst, and marked nervousness and irritability. These signs and symptoms disappeared when his metabolism dropped to minus 25 per cent on iodine, at which time he showed no clinical evidence of myxedema and was

apparently well. Contrasting him with cases 7, 9 and 27, it may be noted that the latter were evidently in a steady state of thyrotoxicosis and their metabolism fell to about the same level each time iodine was given. In case 4 on the other hand, the thyrotoxicosis appeared to be increasing, coincident with a marked increase in the amount of palpable thyroid tissue, and the level to which iodine depressed his metabolism gradually rose.

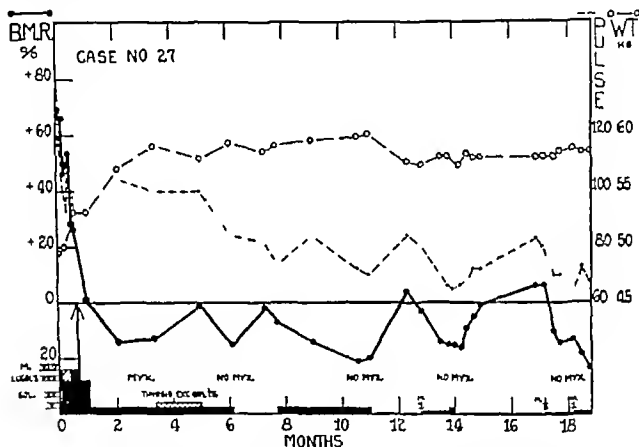


FIG 4 MRS V P, AGE 30 LAB No 4001 REPEATED PRODUCTION OF TEMPORARY LOW METABOLISM COINCIDENT WITH THE ADMINISTRATION AND OMISSION OF IODINE, FOLLOWING SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

Nervousness decreased with each metabolic depression. No myxedema except mild temporary type at the time of the first low metabolism.

Cases 15 (fig 7) and 24, two cases of mild but typical exophthalmic goiter, are outstanding because iodine was the only form of treatment they received for thyrotoxicosis, yet their metabolism fell to a subnormal level, coincident with clinical improvement, on this medication alone. Since collecting this data we have observed the same phenomenon in 2 other cases.

Although there are cases in our series in which iodine was not a factor, the cases elaborated above indicate that iodine can play an important rôle in these temporary metabolic depressions. There is also some suggestive statistical evidence upholding this opinion. On looking up the statistics for 1920 as an example of a year when iodine was not in use as an aid to surgery, it was found that at least 10 per

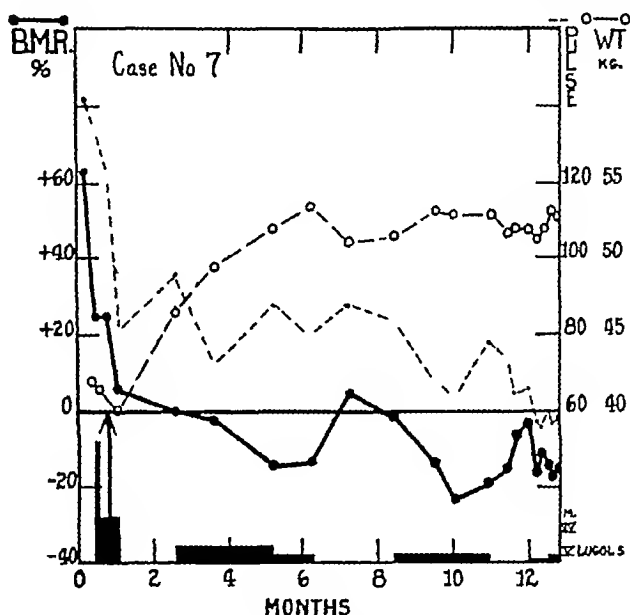


FIG 5 MRS N L, AGE 23 LAB No 4102 ALSO SHOWING REPEATED PRODUCTION OF TEMPORARY LOW METABOLISM COINCIDENT WITH THE ADMINISTRATION AND OMISSION OF IODINE FOLLOWING SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

As in figures 3 and 4, nervousness decreased with each metabolic depression
No myxedema

cent of treated toxic goiter patients developed low metabolic rates, but they were all of the permanent type. The inference is that the use of iodine is the cause of the increase in incidence to about 25 per cent in the years 1925 and 1926, which increase was due mainly to the addition of the temporary type. We are of the opinion that if iodine were not in use, temporary low metabolism would be observed much less frequently.

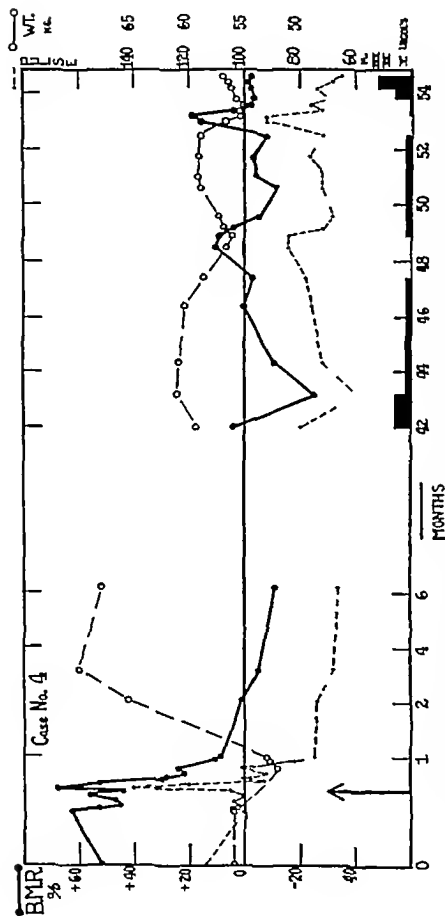


FIG 6 Mr. J W, AOE 40 LAB No 1812 PRODUCTION OF LOW METABOLIC RATE BY IODINE THERAPY 3½ YEARS AFTER SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

No myxedema With a normal metabolism this patient showed well marked symptoms of thyrotoxicosis, which were relieved when the metabolic rate dropped to the low level. The rise and fall of the metabolism on subsequent omission and administration of iodine occurred at progressively higher levels

DISCUSSION

The absence of myxedema in the cases in this study during the period of temporary low metabolism has already been stressed. Hence, if the low metabolism be due to an insufficiency of thyroid secretion, it must be an insufficiency not detectable clinically. There is some reason to suppose that such a clinical state may exist for a short time. We have been much impressed by the length of time

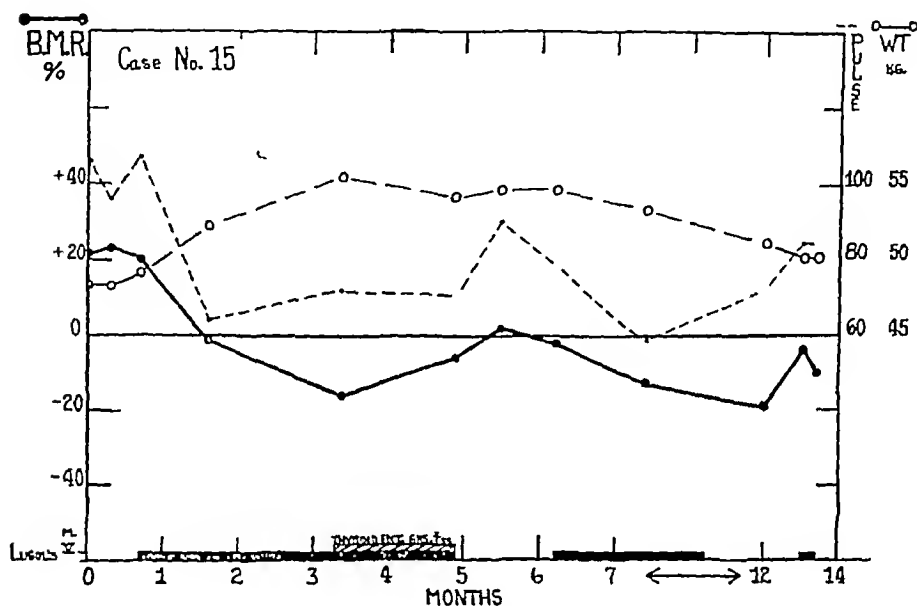


FIG 7 MISS F K, AGE 17 LAB NO 4034 PRODUCTION OF LOW METABOLISM BY THE USE OF IODINE AS THE ONLY TYPE OF TREATMENT IN A CASE OF MILD EXOPHTHALMIC GOITER
No myxedema

necessary for some of our cases of once marked spontaneous myxedema to show any clinical effects of omission of thyroid extract, after they had been kept normal by it for years. It has taken as long as 5 months in one instance. The effect on metabolic rate was noticeable before the clinical effect, nevertheless it also was slow in appearing. It is possible that in some of our cases there was a deficiency of thyroid secretion which lasted for such a short time that the effect was noticeable only on the metabolism and not on the clinical picture.

While very small amounts of *normal* thyroid tissue can keep the body sufficiently supplied with the thyroid hormone, it must be borne in mind that in the cases presented, the gland is a diseased one. It may be that, after treatment, the diseased gland remnant becomes suddenly overburdened and requires a certain length of time to adjust itself to altered working conditions. During this period of adjustment, a mild lack of thyroid secretion might explain the temporary low metabolism in those patients who had a subtotal thyroidectomy.

In view of the considerations just presented, we feel that some of our cases can be satisfactorily accounted for by a period of temporary thyroid insufficiency, not detectable clinically. This will be referred to later.

The hypothesis of a temporary hypothyroidism, however, does not satisfactorily explain

- 1 The striking effect of iodine in repeatedly depressing the metabolism to a subnormal level months to years after operation, coincident with clinical improvement of some signs and symptoms of mild thyrotoxicosis

- 2 The production of a low metabolism by iodine alone when no other form of therapy was used for treatment of thyrotoxicosis

- 3 The development of temporary low metabolism after the removal of only half the thyroid gland. (Four-fifths to seven-eighths of the thyroid may be removed in most cases of toxic goiter without depressing the metabolism to a low level.)

- 4 The occurrence of the low metabolism many months to a few years after operation, and the absence of myxedema in the cases where it lasted many months (fig. 3)

Adjustment of the gland remnant, if it did take place, would naturally occur immediately after operation, and could scarcely account for the onset of a temporary low rate a long time afterwards.

- 5 The fact that temporary low metabolism without myxedema was followed by permanent low metabolism without myxedema in one instance (case 18, fig. 6 in study II (1)).

In connection with the effect of iodine therapy it is important to note that this medication does not appear to ~~alter~~ ^{affect} the metabolism of normal individuals (4) (5) (6) (7), although Marine (8) has made a few observations which suggest that, in a few instances, heat production

may be lowered in normal rabbits by the use of large doses. Careful work on a large series of cases is required in order to settle this point beyond doubt. Present data favor the opinion that iodine therapy does not lower the metabolism of normal people. It may thus be fairly assumed that the depression of the metabolism to a subnormal level by iodine in our cases is associated with the control of thyrotoxicosis. Since no symptoms of myxedema appear, even when the metabolism remains low for several months, it may also be fairly assumed that, in controlling this thyrotoxicosis, iodine does not cause a thyroid insufficiency.

Marine (8) believes that iodine acts in exophthalmic goiter by producing an excess of colloid which blocks the secretion. Such a theory would account for the action of iodine in our series on the basis of a temporary hypothyroidism. This theory appears to be improbable, however, for the following reasons:

- 1 The action of iodine in exophthalmic goiter is well marked before much change in the consistency of the gland has occurred, and is often complete before the storage of colloid reaches its maximum.

- 2 We have seen the metabolism rise when iodine was continued after producing its usual remission, in spite of the persistence of such an excess of colloid that the gland was stony hard.

The foregoing considerations lead up to a second explanation for temporary low metabolism, which appears to be more adequate than temporary hypothyroidism to account for many of our cases. The assumption is that the normal basal metabolism of the patients concerned is low. A certain number of normal people who have never had thyrotoxicosis have a basal metabolism in the vicinity of minus 16 to minus 25 per cent; consequently a low metabolism without myxedema occurring after treatment for toxic goiter may be explained very well as a drop to the patient's normal level, similar to that commonly occurring in a patient whose normal level is in the vicinity of zero. Just as the latter phenomenon is probably increased in incidence by the use of iodine during the immediate post-operative period, so also is the former. Just as patients whose metabolism drops to its normal level of about zero often develop, especially if iodine be omitted, a slightly elevated metabolism of about plus 20 per cent, with no very definitely discernible symptoms of thyrotoxicosis, so also may

patients whose metabolism drops to its normal low level of about minus 20 per cent shortly develop the same clinical picture, with a metabolic rate of about zero. This may occur in spite of iodine therapy, but is much more likely to occur if iodine be omitted. It may occur also, in the natural course of events, when iodine has never been used at any time. Then, just as in the first group, this residual thyrotoxicosis may eventually burn itself out, allowing the metabolism to return to the vicinity of zero, so also may the same train of events occur in the latter group, allowing the metabolism to return to its normal level of about minus 20 per cent. Accordingly, some of our temporary low rate cases without myxedema, which at present show a standard normal metabolism may eventually develop a permanent low metabolism without myxedema, as is very definitely suggested by case 18 (see fig. 6 in study II (1)).

The hypothesis that a metabolism below the standard normal level may be normal for some individuals will be discussed in more detail in the paper on permanent low metabolism without myxedema (1).

There are a few cases in our series which seem to be exceptions to this hypothesis, i. e., those in which the metabolism was below minus 25 per cent. We have never seen individuals who could be considered normal with a metabolic rate lower than this. Thus, in at least these cases, the transient low rate appears to be explained best by a temporary lack of normal thyroid secretion, not detectable clinically. The same explanation may also hold for a few of the cases in which the lowest metabolism recorded was above minus 25 per cent.

The number of cases in which the low metabolism was due to temporary hypothyroidism and the number in which it represented the normal metabolic level of the patient, can be definitely determined only by following the patients until their metabolism has reached a stationary level.

Aside from attempting to explain the significance of temporary low metabolism and the mechanism by which it may occur, there is a point of minor interest brought out by the data collected, viz., in connection with thyroid therapy. In view of the striking lack of myxedema in our group of cases, we wish to emphasize the importance of treating the signs and symptoms of that deficiency rather than the metabolic rate. In the past, patients with a metabolic rate below

minus 15 per cent have often been assumed to have myxedema, and they have in many instances been put on thyroid extract merely because of the reduced metabolism, even though there were no signs nor symptoms of hypothyroidism. This medication has been sometimes continued unnecessarily for years, because the possible lack of correlation between the low metabolism and myxedema was not recognized, aside altogether from the fact that the low metabolism itself might be only temporary.

SUMMARY

Twenty-seven cases have been presented showing temporary low metabolism (minus 16 to minus 44 per cent) without myxedema, following treatment for thyrotoxicosis.

The usual time of onset of this low metabolism was within 4 months after treatment, although in a few cases it was from 1 to 3½ years afterwards. The usual duration was about 1 to 4 months.

During the period of low metabolism, most of the patients appeared to be normal individuals.

It occurred after x-ray therapy and after subtotal and hemithyroidectomy.

In 5 cases there was no iodine therapy during the period of low metabolism. In 7 cases, the metabolism both fell and rose on iodine, and in 15 cases (including 2 in which neither surgery nor x-ray therapy was employed) the metabolism fell on iodine and rose when it was omitted. In some of the latter cases, months to years after operation, the metabolism could be made to fluctuate at will from a standard normal to a subnormal level and back again, by the administration and omission of iodine.

In some instances, signs and symptoms diagnostic of or suggestive of mild thyrotoxicosis, which were present with a standard normal metabolic rate, disappeared when iodine was given and the metabolism dropped to a subnormal level.

CONCLUSION

In some cases, temporary low metabolism without myxedema following thyrotoxicosis appears to be due to a period of thyroid insuffi-

ciency not detectable clinically. In others, it appears to represent a transient return to the patient's normal metabolic level, the subsequent rise to standard normal metabolism representing a period of mild recurring thyrotoxicosis.

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LOW BASAL METABOLISM FOLLOWING THYROTOXICOSIS

II PERMANENT TYPE WITHOUT MYXEDEMA¹

By WILLARD OWEN THOMPSON² AND PHEBE K. THOMPSON³

(From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital)

INTRODUCTION

As outlined in part I of this study (1), in the course of an investigation of the surprising number of low metabolisms observed following thyrotoxicosis, it was found that approximately half were of the temporary type and half of the permanent type and moreover, that about two-thirds of the latter group showed no clinical evidence of myxedema⁴. It is our purpose in this paper to present a study of permanent low metabolism without myxedema. The data on temporary and permanent myxedema following thyrotoxicosis, are to be presented later (2).

Although there are a few reports in the literature on low metabolism without myxedema, there are no studies of this phenomenon following thyrotoxicosis.

METHOD AND MATERIAL

For the method used, see part I of this study (1).

Included in this series are 21 patients who, without clinical evidence of myxedema, had a low metabolic rate, presumably of the permanent type, ranging from minus 16 to about minus 25 per cent, after recovery from thyrotoxicosis. In 14 instances the metabolism was followed long enough and closely enough to indicate that it would remain perma-

¹ This study was aided in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

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⁴ The term "myxedema" is used to denote any degree of true thyroid deficiency which is clinically discernible. It is not limited to the full blown typical picture.

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TABLE 1
Twenty one cases showing permanent low metabolism without myxedema, following thyrotoxicosis

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
1	Mrs A G (see fig 2)		per cent		kgm		
2*	Exophthalmic goiter	December 2, 1924	+51	128	57 4	Lugol's solution M XV daily	Moderate thyrotoxicosis for 6 months
		December 8, 1924	+18	100	57 4		Goiter + Slight exophthalmos
		December 10, 1924				<i>Subtotal thyroidectomy</i>	Tremor + Loss of 15 pounds
	Mrs L C Age 47	December 20, 1924				Lugol's decreased to M V daily	No thyrotoxicosis
	Lab No 2940	December 22, 1924	-6	70	57 4	Lugol's omitted	
		January 27, 1925	-10	72	60 6		Very well
		March 3, 1925	-16	64	61 0		Mild myxedema
		May 2, 1925	-25	62	58 7	Thyroid extract (Burroughs Wellcome) grains Iss daily	Improved
		May 14, 1925	-21	68	59 3	Thyroid increased to grains Iss and III on alternate days	
		May 29, 1925	-17	64	58 6	Thyroid increased to grains III daily	
		June 25, 1925	-11	65	59 5		
		August 27, 1925	-19	68	58 8	Thyroid increased to grains IV daily	No myxedema
		October 28, 1925	-14	72	60 6		Well
		December 31, 1925	-7	68	60 6		
		March 25, 1926	-9	78	61 8		
		June 23, 1926	-9	72	58 5		
		October 28, 1926	-17	74	60 7		Perfectly well

	December 2, 1926 January 6 1927 February 19 1927 March 19 1927 April 2 1927 May 14 1927 July 12 1927 August 15, 1927 October 22, 1927	-12 -15 -17 -22 -18 -28 -24 -20 -18	68 60 7 74 58 7 76 60 6 64 60 6 72 60 3 66 59 0 72 58 0 68 57 7 68 58 3	Thyroid omitted Thyroid extract grains I daily Thyroid decreased to grains 25 daily Thyroid omitted	Perfectly well Just as well as when on thyroid. No myxedema No change No myxedema Perfectly well
3	Mrs. A. A., (see fig 1 and case history on page 486)				
4	Mrs. M. H. (see fig 4)				
5	Mrs. E. W. (see fig 3)				
6	Exophthalmic goiter Mrs. O. McC. Age 32 Lab. No 3023	+45 +22 +11 February 8, 1925 February 11, 1925 February 13, 1925 February 16 1925	112 40 1 94 41 0 84 41 0 72 41 4	Lugol's solution M XV daily <i>Subtotal thyroidectomy</i> Lugol's increased to M XLV daily Lugol's decreased to M XXX daily Lugol's decreased to M XX daily Lugol's decreased to M. XV daily	Moderate thyrotoxicosis 2 months. Goiter + Slight exophthalmos. Tremor + Lost 17 pounds in 6 months

* We wish to thank Dr J. H. Means for the use of the data on this case and on cases 8 and 19

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
6	Exophthalmic goiter	February 17, 1925				Lugol's omitted NaI (saturated solution) M V every other day	Much improved
		February 18, 1925					
	Mrs O McC Age 32 I ab No 3023	March 24, 1925	-19	70	43 4	NaI, M V daily every other week	No thyrotoxicosis No myxedema
		May 27, 1925	-11	74	45 1	NaI omitted	Well Slightly nervous
		November 12, 1926	-18	68	47 5	Lugol's solution M V daily	No myxedema
		June 26, 1925	+13	85	40 1	On potassium iodide	Mild thyrotoxicosis for 3 years
7	Toxic adenoma	July 1, 1925	-3	78	40 0	Iodide omitted	Goiter + Tremor + Nervousness Palpitation ++
		July 10, 1925				<i>Left hemithyroidectomy</i>	No change since operation
	Mrs J E Age 28 Lab No 3338	September, 1925					
		December 1, 1925	-22	76	42 1		
		December 14, 1925	-20	72	42 4	Thyroid extract (Armour's) grains Iss daily	No myxedema Nervous
		December 24, 1925	-13	68	43 2	Thyroid increased to grains III daily	? Improvement
		February 8, 1926	-21	82	44 9	Thyroid decreased to grains Iss daily	
		March 30, 1926	-8	76	46 5	Thyroid decreased to grains I daily	Very nervous Pregnant
		April 15, 1926	-5	84	47 7		
		June 21, 1926	+9	87	51 1		Well
		August, 1926				Thyroid omitted	Parturition
		September 24, 1926	-13	74	45 1	Thyroid grains Iss daily	

						Thyroid omitted			
8	Exophthalmic goiter Mrs. P. T. Age 26 Lab. No. 615		October 15, 1926	-1	68	46	4	Thyroid omitted	Nervous No myxedema No myxedema
			November 5, 1926	-16	72	48	8		
			December 31, 1926	-19	64	49	3		
			April 1, 1927	-28	56	49	2		
			June 24, 1927	+10	94	48	0	Double ligation of superior thyroid arteries	Thyrototoxicosis for 1 year Eyes stary Goiter + Palpitation ++ Perspiration ++ Persistent thyrototoxicosis
			May 21, 1920	+66	120	54	0		
			April 5, 1923	+38	126	55	5		
			April 25, 1923	+37	106	52	5		
			April 27, 1923	+30	115	51	5	Subtotal thyroidectomy	Very well. No myxedema Very well. No myxedema
			May 3, 1923	+32	112	52	2		
			May 11, 1923	+7	88				
			May 17, 1923	+26	110				
			May 18, 1923	+20	93	53	0	Thyroid extract grains IX daily	Goiter + Exophthalmos + Tachycardia. Tremor Weakness Goiter and exophthalmos. Weakness chief complaint. No myxedema
			May 19, 1923	-28	76	66	7		
			May 22, 1923	-14	74	63	1		
			May 23, 1923						
9	Exophthalmic goiter Mrs. L. W. Age 49 Lab. No. 1927		May 26, 1925	-5	72	71	0	Thyroid extract grains IX daily	
			March 10, 1927	-22	65	72	0		
			1913 to 1915	-35	65	72	0		
			March 31, 1923	-29	60	72	0		
			April 2, 1923	-5	72	71	0		
			April 5, 1923						
			April 6, 1923						

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate		Pulse		Weight	Treatment	Clinical notes
			per cent	rate			kgm		
9	Exophthalmic goiter Mrs L. W. Age 49 Lab No 1927	April 23, 1923	-21		67	70 0		Thyroid omitted	
		May 9, 1923	+8		100	68 0		Thyroid extract grains IX daily	
		June 5, 1923	-1		80	68 5		Thyroid decreased to grains III and IVss on alternate days	Palpitation and trembling
		August 7, 1923	±0		65	71 0		Thyroid increased to grains IVss daily	
		November 1, 1923	-6		92	70 0		Thyroid decreased to grains III daily	Weak spells
		January 3, 1924	+8		64	69 0			
		March 7, 1924	-9		80	69 5			
		April 5, 1924	+2		68	69 5			
		May 29, 1924	±0		68	71 0			Weak and listless
		June 28, 1924	+1						
		September 6, 1924						Thyroid omitted	
		October 29, 1924	-10		70	74 0		Thyroid extract grains III daily	
		November 8, 1924	-7		64	71 8			
		February 7, 1925	-7		64	73 5			
		June 7, 1925	-8		76	74 0			Weak spells
		August 29, 1925	-10		72	76 7		Thyroid increased by grains Iss every third day	
		December 19, 1925	+1		72	74 9		Thyroid decreased grains Iss every other day	Better than ever before
		March 20, 1926	-13		76	76 1		Thyroid increased to grains III daily	Tired and dopy, but no myxedema
		April 24, 1926						Thyroid omitted	
		October 7, 1926							

10	Exophthalmic goiter Mr E. J Age 30 Lab No 3135	<p>October 30 1926 -5 64 77 9 November 13, 1926 -7 96 77 9 December 3, 1926 -10 76 77 3 December 18, 1926 -18 78 77 1 January 8 1927 -2 74 78 0 February 12, 1927 +17 92 76 6 April 2, 1927 +5 112 73 7 June 11, 1927 -5 114 74 7</p> <p>March 25, 1925 +55 96 56 6 March 26, 1925 April 3 1925 +25 86 57 4 April 6, 1925</p> <p>April 9, 1925 -4 70 58 0 April 22, 1925 -5 72 60 3 May 22, 1925 -14 68 66 7 April 27 1926 -16 72 67 4 May 11, 1926</p> <p>May 27, 1926 -6 83 65 1</p> <p>June 28, 1926 -17 72 66 9 July 26, 1926 -29 75 67 7 September 13, 1926 -13 74 65 7 October 23, 1926 -12 68 62 3 December 18, 1926 -14 59 62 1 January 15, 1927 -15 63 63 7</p>	<p>Thyroid extract (Armour's) grains III daily Thyroid decreased to grains Iss daily</p> <p>Lugol's solution M XV daily</p> <p><i>Subtotal thyroidectomy</i> Lugol's increased to M LX daily Lugol's decreased to M XV daily Lugol's omitted</p> <p>Lugol's M XXX daily Lugol's decreased to M. V daily Started thyroid extract (Armour's) grains III daily Thyroid decreased to grains Iss daily Lugol's decreased to M. V daily Thyroid omitted</p> <p>Thyroid grains III daily Thyroid omitted</p>	<p>No change. No myxedema</p> <p>No change except muddled cold less</p> <p>Mild thyrotoxicosis for 2 years. Goiter + Tremor + Exophthalmos + Lost 34 pounds in 6 years</p> <p>Much improved</p> <p>No thyrotoxicosis No myxedema</p> <p>Doubtful improvement on thyroid</p> <p>Doubtful improvement on thyroid</p>
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TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
10	Exophthalmic goiter Mr E J Age 30 Lab No 3135	February 12, 1927	per cent -9	80	63.4	Lugol's omitted	Well
		March 12, 1927	-23	74	63.4		Well No myxedema
		April 23, 1927	-14	70	65.3		No change since omission of Lugol's
		May 27, 1927	-9	72	65.0		Well
		July 5, 1927	-12	64	65.1		
			+43	103	45.5	First x-ray treatment	Moderate thyrotoxicosis about 1 year
11	Exophthalmic goiter Mrs E G Age 48 Lab No 1311	February 13, 1922	+45	100	45.0	Second x-ray treatment	Goiter + Exophthalmos + Tremor + Lost 17 pounds in 2 months
		February 15, 1922				Third x-ray treatment	Improved
		March 8, 1922				Fourth x-ray treatment	
		March 29, 1922				Fifth x-ray treatment	
		March 30, 1922	+32	101	51.0		
		April 26, 1922	+13	85	49.5		
		April 27, 1922	+16	83	49.0		
		May 17, 1922	+19	82	48.0		
		June 6, 1922				Sixth x-ray treatment	
		July 14, 1922				Seventh x-ray treatment	
		July 19, 1922				Eighth x-ray treatment	
		August 16, 1922	+27	114	50.0		
		September 6, 1922	+11	76	50.0		
		September 21, 1922					Headaches. No menses for 5 months
		October, 1925					

12	Toxic adenoma Mrs. M. B. Age 38 Lab. No 348	November 4 1925	-17	64 62 3	Improved No myxedema, but tired all the time No myxedema
		November 12, 1925	-16	64 62 5	
		November 15 1926	-15	72 64 6	Lugol's solution M. X daily Thyroid extract (Armour's) grains IVas daily
		November 30, 1926	-6	66 64 3	
		January 6 1927	-4	74 62 5	Lugol's decreased to M V daily Thyroid increased to grains VI daily
		February 7, 1927	+3	68 61 6	
		March 21, 1927	-6	72 63 3	Thyroid decreased to grains Ias daily Thyroid increased to grains III daily
		May 17, 1927	±0	68 65 0	
		October 7 1919	+50	116 39 0	First x-ray treatment Second x-ray treatment Third x-ray treatment Fourth x-ray treatment Fifth x-ray treatment Sixth x-ray treatment
		October 27, 1919			
		November 19, 1919	+52	100 42 0	Thyroid extract grains IVas daily Thyroid omitted
		December 15, 1919			
		January 5, 1920			Thyroid extract grains IVas daily Thyroid omitted
		January 26, 1920			
		February 25, 1920	+18	80 47 0	Myxedema Normal again
		September 29 1920	-3	66 48 5	
		February 25, 1921	-6	64 50 5	Perfectly well
		August 29, 1921	-35	40 48 0	
		September 15, 1921	+2	61 45 5	
		October 27 1921			
		October 31, 1921	-13	60 46 0	
		January 10, 1922	-1	63 46 0	
		March 7, 1922	±0	57 46 0	

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
12	Toxic adenoma Mrs M B Age 38 Lab No 348	June 10, 1922					
		July 3, 1922		61	47.0	Thyroid omitted	
		August 15, 1922	-23			Thyroid grains IVss daily	Myxedematous again
		September 7, 1922	-23	60	46.0	Thyroid omitted	Myxedematous
		February 8, 1926	+3	72	43.3	Thyroid grains IVss daily Thyroid decreased to grains III daily	Excellent condition No myxedema
		November 10, 1926	-11	64	45.5	Thyroid omitted	
		November 30, 1926	-8	58	45.9		
		December 21, 1926	-8	68	46.0		
		January 4, 1927	-13	62	45.6		
		January 27, 1927	-19	56	46.3		
		February 15, 1927	-17	60	45.9		
		March 8, 1927	-23	56	46.5		
		April 26, 1927	±0	68	47.1		
		June 7, 1927	-12	64	45.7		
		June 21, 1927	-8	64	45.7		
		July 19, 1927	-15	64	45.7		
		August 9, 1927	-8	60	46.0		Perfectly well No myxedema
13	Droptthalmic gout Mrs L E Age 43 Lab No 4383	December 9, 1926	+88	130	49.9	Lugol's solution M XLV daily	Moderate thyrotoxicosis 1½ years
		December 15, 1926	+37	105	49.9		Gout + Exophthalmos +
		December 19, 1926				Lugol's decreased to M XXX daily	Tremor + Lost 40 pounds in 1 year
		December 23, 1926				Lugol's decreased to M XV daily	
		December 24, 1926	+13	80	47.5	Subtotal thyroidectomy	

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
15	Exophthalmic goiter Mrs D C Age 32 I ab No 3980	June 19, 1926			kgm	Lugol's decreased to M V daily	Improved
		July 28, 1926				Lugol's increased to M XXX daily	
		July 29, 1926				Lugol's increased to M XL daily	
		July 30, 1926				<i>Left hemithyroidectomy</i>	Much improved cosis ? Mild myxedema
		July 31, 1926				Lugol's increased to M LX daily	
		August 7, 1926				Lugol's decreased to M XXX daily	
			+9	115	35 3	Lugol's decreased to M XV daily	? Mild myxedema ? Mild myxedema
		September 22, 1926	-21	73	43 9	Lugol's decreased to M V daily	
		October 22, 1926	-15	74	45 5	Thyroid extract (Armour's) grains IVss daily	
		November 6, 1926	+10	92	44 3	Thyroid decreased to grains Iss daily	Myxedema practically gone
		December 4, 1926	-5	76	44 3	Thyroid omitted	
		December 30, 1926	-7	72	45 6	Thyroid continued	
		February 5, 1927	-16	84	47 2	Thyroid extract grains III daily	Perfectly well Perfectly well ? Mild myxedema, less marked than in September, 1926 No myxedema Well
		February 19, 1927	-11	88	46 5	Thyroid decreased to grains Iss daily	
		April 2, 1927	-9	96	46 9	Thyroid continued	
		May 7, 1927	-11	68	48 0	Thyroid omitted	Lugol's continued

16	Exophthalmic golfer	June 11, 1927	-18	78	48	9	Lugol's omitted	Better than ever in her life No myxedema
		July 2, 1927	-12	86	47	9	Lugol's M V daily	No myxedema
		July 23, 1927	-12	70	48	5		Perfectly well. No myxedema
		August 6, 1927	-18	72	48	7		
		August 20, 1927	-24	72	49	1		
		October 15, 1927	-22	74	51	1	Lugol's omitted	
			+38	103	45	7		Moderate thyrotoxicosis 3 months.
		July 23, 1925	+39	96	45	5	Lugol's solution M VXX daily	Slight exophthalmos. Golfer +
		July 28, 1925	+39	84	44	6		Tremor + Lost 30 pounds in
		July 30, 1925	+18	84	44	9		9 months
	Mrs. M F	August 2, 1925					Lugol's omitted	
	Age 33	August 6, 1925					<i>Subtotal thyroidectomy</i>	
	Lab No 3399	August 7, 1925						
		August 22, 1925	+6	76	46	0		
		September 8, 1925	-7	68	46	9		
		October 13, 1925	±0	74	49	2		
		April 20, 1926	-10	74	52	0	Lugol's M V daily	
		May 7, 1926	-16	70	53	1	Lugol's increased to M VXX daily	No myxedema. Slight residual thyrotoxicosis
								Less nervous
		May 18, 1926	-18	60	53	9	Lugol's decreased to M V daily	
		May 25, 1926	-13	55	54	3	Thyroid extract (Armour's) grains 1/2 daily	Definite improvement
		June 7, 1926	-12	61	53	7	Thyroid increased to grains IVs	
		June 28, 1926	-5	59	51	5	daily	
		July 12, 1926	+4	66	50	9	Lugol's omitted	
		July 27, 1926	+2	72	50	6		
		September 1, 1926					Thyroid omitted	
		November 9, 1926	-7	68	52	5	Lugol's M VXX daily	Well
		December 3, 1926	-12	61	53	6	Lugol's decreased to M V daily	Severe cold for 3 weeks
		January 18, 1927	-7	65	50	5	Thyroid extract grains IVs daily	Well
		February 25, 1927	+6	72	50	3		Tired
		April 21, 1927	+2	76	48	5	Thyroid omitted. Lugol's con tinued	Well. Less tired
		June 7, 1927	-14	66	51	7		Easily tired. No myxedema
		July 11, 1927	-17	72	51	5	Thyroid grains 1/2 daily	

TABLE 1—Continued

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
			per cent		kgm.		
17	Exophthalmic goiter	June 11, 1925	+62	124	53.8	Lugol's solution M XXXX daily	Moderate thyrotoxicosis 6 months + Goiter + Exophthalmos + Tremor +
		June 13, 1925	+63	110	53.2		
		June 14, 1925	+49	118	52.3		
		June 17, 1925	+33	96	51.8		
	Miss I C Age 23 Lab No 3303	June 19, 1925	+37	96	52.0	<i>Subtotal thyroidectomy</i> Lugol's increased to M LX daily Lugol's decreased to M XXXX daily Lugol's omitted. Started NaI (saturated solution) M V every other day	Much improved
		June 21, 1925	+20	82	52.2		
		June 23, 1925					
		June 26, 1925					
		July 3, 1925	-9	61	52.5	NaI omitted	No thyrotoxicosis No myxedema
		July 24, 1925	-13	79	55.6		
		August 6, 1925	-15	59	59.2		
		August 22, 1925	-16	63	63.5		
		September 16, 1925	-19	70	60.7	KI M V daily	No myxedema
		October 14, 1925	-19	65	61.5		
		November 1, 1925	-12	80	61.7		
		November 13, 1925	-18	61	60.9		
		November 20, 1925	-17	67	62.3	Thyroid extract (Armour's) grains IX daily	No change
		December 1, 1925	-16	72	62.3		
		December 10, 1925	-15	67	62.5		
		December 15, 1925	-6	80	60.5	Thyroid decreased to grains III daily KI continued	? Improvement. No thyrotoxicosis Well

18	Exophthalmic goiter Miss C. A. Age 16 Lab. No. 200	February 5, 1919 February 13, 1919 October 25, 1919 June 4, 1920 October 18, 1921 January, 1922 August 2, 1923	+40 -5 -10 -8 -19	63 0 78 72 5 76 71 7 67 72 5 68 80 0	Subtotal thyroidectomy Double oophorectomy for ovarian cyst	Mild thyrotoxicosis about 1 year Goiter + Slight exophthalmos. Tremor + Loss of 20 pounds in 1 month Well Well. No myxedema
19	Exophthalmic goiter Mr. W. A. H. Age 64 Lab. No. 1518	June 8, 1922 July 7, 1922 July 8, 1922 July 14, 1922 September 22, 1922 January 27, 1923 May 26, 1927	+31 +66 +47 +8 +6 -25	85 49 5 80 48 4 70 47 0 48 57 5 50 59 0 52 59 0	(In another hospital) Subtotal thyroidectomy	Moderate thyrotoxicosis for 3 years. Exophthalmos + Tremor + Rapid weight loss. Goiter not visible No thyrotoxicosis Doing well No myxedema. No thyrotoxicosis. Moderate arteriosclerosis
20	Exophthalmic goiter Mrs. D. H. Age 40 Lab. No. 702	January 20, 1919 January 28, 1919 November 10, 1919 February 21, 1922 September 21, 1922	+16 -8 -8 -17	84 52 5 80 53 0 70 50 5 66 48 0	Left hemithyroidectomy	Mild thyrotoxicosis 6 months. Goiter + Tremor + No eye signs. Lost 14 pounds in 6 months Much improved. No thyrotoxicosis. No myxedema
21	Exophthalmic goiter Mrs. M. H. Age 44 Lab. No. 596	1903 April 24, 1920 April 29, 1920 May 17, 1920 October 26, 1921	+27 +9 -17	96 57 0 100 56 5 81 79 0	Double oophorectomy Subtotal thyroidectomy	Moderate thyrotoxicosis about 6 months. Goiter + Exophthalmos + Tremor + Lost 35 pounds in 6 months Very well since operation No myxedema

nently at a low level without medication. In 3 others, iodine was administered throughout most of the period of observation, thus rendering the permanency of the low metabolism somewhat uncertain. In this group of 17 patients there are 6 who, shortly after treatment, had signs and symptoms either suggestive of or actually diagnostic of myxedema. These manifestations were only transient. At present, without medication, these patients show no evidence of myxedema, although they have low metabolic rates. They therefore have been listed as cases of permanent low metabolism without myxedema. There are in addition to these 17 cases 4 others, not on iodine, whose low metabolism determinations were too few to establish their permanency, but on account of the considerable length of time they were observed after treatment they probably belong to this group.

Table 1 gives an outline of the basal metabolic and clinical histories on those of the 21 cases on whom the data is not charted.

Time of onset

In 7 cases the onset of the permanent low metabolism was within 3 months after treatment; in 4 cases it was within 3 months to 1 year, and in 3 cases it was over 1 year after treatment. In 7 cases the time of onset was unknown.

Absence of myxedema

The main issue with regard to permanent low metabolism is whether it is normal or abnormal for the patients concerned. This must be decided upon the basis of the accompanying clinical picture. The striking thing about the patients presented in this study was the absence of signs and symptoms of myxedema, as illustrated by a typical case history.

Case 3⁵ (fig 1) Lab No 819 Age 44 in 1920. In 1912 she developed typical exophthalmic goiter, for which a partial thyroidectomy was performed in another hospital in March, 1913. After operation her symptoms were exaggerated, but

⁵ The early data on this and 3 other cases have been reported before as follows:

Cases 3 and 12: Holmes, *Am Jour Roent*, 1921, viii, 730, and Means and Holmes, *Arch Int Med*, xxxi, 303, 1923.

Case 4: Holmes, *ibid*.

Case 5: Richardson and Means, *Arch Surg*, 1924, ix, 237.

began to improve about 2 years later. In December, 1920, when first seen in this hospital, her basal metabolic rate was plus 50 per cent and her pulse 100. Her thyroid was diffusely enlarged. She had slight exophthalmos, marked tremor, palpitation and dyspnea. She was hoarse, her mucous membranes were slightly pale, her skin was dry and she had brown pigmentation of hands, axillae, groins and genitals. The diagnoses were post-operative exophthalmic goiter and cardiac decompensation. She was given 5 x ray treatments during the period December, 1920, to March, 1921, and her basal metabolic rate dropped to normal. In October she was reported as having done well all summer. In November, 1921, there was some recurrence of thyrotoxicosis with a basal metabolic rate of plus 31 per cent. Three more x ray treatments were given November, 1921, to January, 1922. Her basal metabolic rate again dropped to normal and she was symptom free.

She felt well until September, 1924, when she developed symptoms from uterine fibroids, for which she had a hysterectomy and double salpingo-oophorectomy performed during the same month. No metabolisms were done between January, 1922, and April, 1925. On the latter date, 3 years after her x ray treatment for toxic goiter and 6 months after her pelvic operation, her basal metabolic rate was minus 21 per cent, and continued at about this level during the following two months. She was prevailed upon to enter the hospital for study. She had gained 3 kgm since 1922. Her hair was slightly dry and her skin was pigmented, as previously described when she had thyrotoxicosis in 1920. Her tongue was not particularly thick. Her memory was good. Her appetite was good. Her speech was rather slow, but the patient said this was natural for her. There was no abnormal weakness or fatigue, no marked palpitation or dyspnea on exertion, no headaches and no dizziness. The palms and soles of her feet sweated profusely. Her ankles swelled only if on her feet all day. She had a large dilated heart. There was no clinical evidence of myxedema. She felt well and insisted that she did not need to be in a hospital.

She was put on thyroid extract, 6 grains daily. In 5 days' time her rate was minus 17 per cent. Thyroid was decreased to 3 grains daily, on which dose her metabolism remained practically unchanged. Thyroid was increased to 6 grains daily on several subsequent occasions, but each time caused palpitation, sweating, insomnia and hot flashes, and had to be decreased. There was no significant effect on metabolism, and no clinical improvement occurred. Her basal metabolic rate remained at about minus 21 per cent up to January, 1926. Thyroid was omitted in February, 1926. In November, 10 months later, her rate was minus 25 per cent. She looked and felt exceptionally well. She was strong, not easily fatigued and not sensitive to cold. Her appetite was very good. Her hair was slightly dry. Her speech was somewhat slow but not thick. There was no edema. In short, there was no evidence of hypothyroidism. Thyroid extract, 3 grains daily, was started again. She took it for about one month with no clinical results, except that she experienced occasional hot flashes. In April, 1927, when 4 months

off thyroid, she was apparently quite normal, with no symptoms of myxedema, although her metabolism was minus 24 per cent. She stated that she had hot flashes only when on thyroid. Ovarian extract, grains V, three times daily, was given although there was no indication for it clinically. It produced no change.

Most of our cases were like the one just presented during the period of their low metabolism, e g, figures 2 and 3. They were alert, ener-

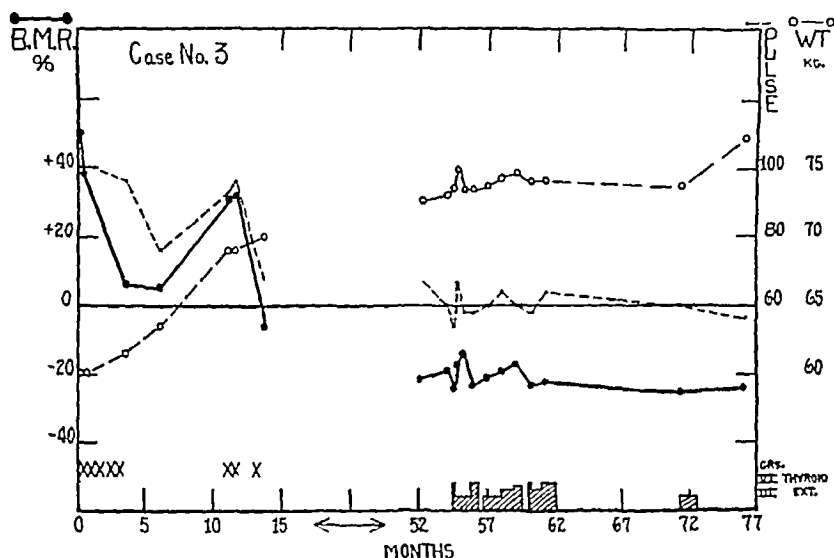


FIG 1 MRS A A, AGE 44 LAB NO 819 PERMANENT LOW METABOLISM WITHOUT MYXEDEMA, FIRST OBSERVED THREE AND ONE-QUARTER YEARS AFTER TERMINATION OF X-RAY TREATMENT (X), AND TWELVE YEARS AFTER HEMIHYROIDECTOMY FOR EXOPHTHALMIC GOITER

Double oophorectomy performed 6 months before low metabolism was observed. Six grains of thyroid extract daily did not significantly affect the basal metabolism, but caused symptoms of thyroid intoxication. (In this and subsequent figures cross-hatched areas denote thyroid therapy.)

getic individuals who did not tire easily and were not sensitive to cold. Their skin was soft and smooth, there was no edema and their hair was not dry. Mrs E C (case 2, table 1), for example, worked daily from 6 00 a m to 9 30 p m. Besides doing all the housework in an eight-room house, she was able to take care of a small garden and do most of the work in connection with about 300 chickens, as well

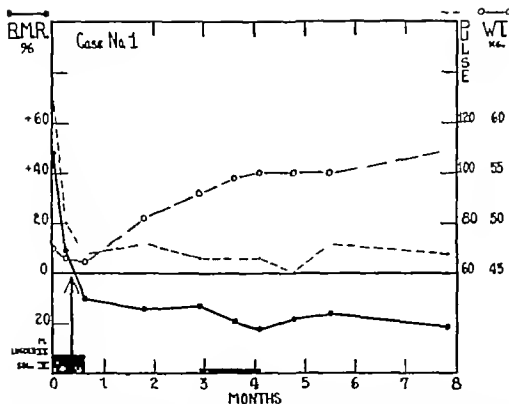


FIG 2 MRS A G, AGE 42 LAB NO 4549 PERMANENT LOW METABOLISM WITHOUT MYXEDEMA FOLLOWING SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

The metabolism remained low after omission of iodine, in contrast to what happens in cases of temporary low metabolism, as shown in figures 4 and 5 in Part I of this study (1) (In this and subsequent figures, black areas denote Lugol's therapy)

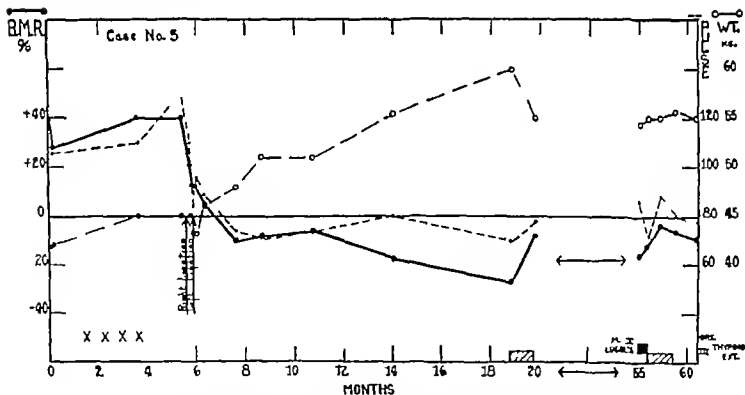


FIG 3 MRS E W AGE 22 LAB NO 1432 PERMANENT LOW METABOLISM WITHOUT MYXEDEMA FOLLOWING RAY TREATMENT (V) AND DOUBLE LIGATION FOR EXOPHTHALMIC GOITER

Thyroid therapy did not produce any clinical change

as serve on several church and civic committees All these activities produced only slight fatigue, which was not increased by omission of thyroid extract This medication in moderate doses raised her metabolism only slightly

A few of the cases, viz , cases 4 (fig 4), 7, 9, 10, 11 and 16, while they did not have myxedema, were slightly different from those just described

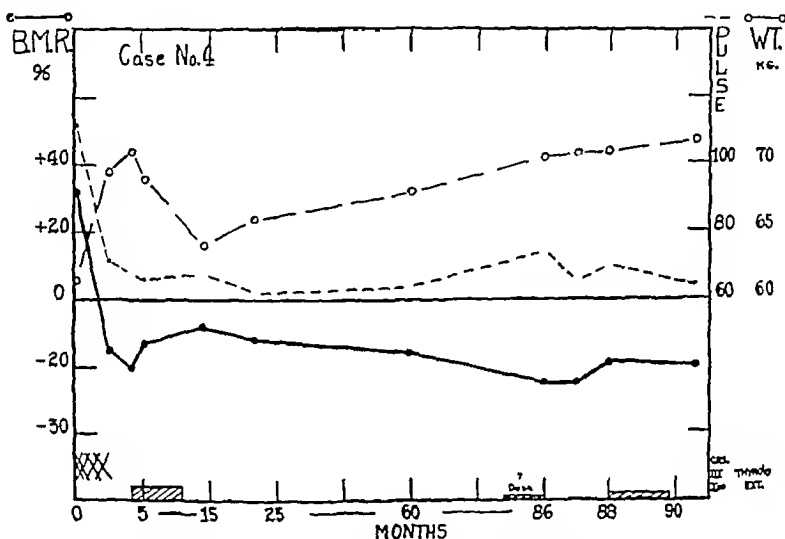


FIG 4 MRS M H, AGE 37 LAB NO 575 PERMANENT LOW METABOLISM FOLLOWING X-RAY TREATMENT (X) FOR EXOPHTHALMIC GOITER

Question of mild myxedema during first 3 months after termination of treatment No myxedema with a low basal metabolic rate, 2, 5, 7 and 7½ years after treatment

Case 4 (fig 4) is fairly typical of the group At the time of her low metabolism, which ranged for the most part between minus 20 and minus 25 per cent, she was nervous and excitable, tired easily, and was sensitive to cold Her skin, however, was soft and warm, her hair was not dry and there was no edema She was definitely not myxedematous Thyroid extract in doses of $1\frac{1}{2}$ grains daily produced no effect on her metabolism, but, while taking it, she thought she tired a little less easily and was less nervous No objective changes were discernible The other patients of this type on whom thyroid

extract was tried felt a little better at times while taking it, but at other times no improvement was noted. This whole group resembled patients with very mild thyrotoxicosis rather than those with myxedema.

Relation of permanent low metabolism to some pathological entities other than myxedema

Myxedema is of course not the only abnormality associated with low metabolism. The latter may be observed for example in conditions of starvation, in chronic nephrosis, and in deficiency of endocrines such as anterior pituitary or adrenal cortex. These disorders were not factors in any of our cases.

A low metabolism is often attributed to hypogonadism because the two are sometimes found to be associated. Inasmuch as this idea is prevalent, those of our cases are cited below in which there was a history of either double oophorectomy or of the occurrence of the menopause. They appeared to be normal individuals and showed no symptoms known to be associated with ovarian deficiency.

Case 18 (table 1), had a thyroidectomy in February, 1919. Her metabolism was minus 10 per cent in 1920. A double oophorectomy was performed in January, 1922. The only metabolism determination thereafter was minus 19 per cent in August, 1923.

Case 21 (table 1) had a double oophorectomy in 1903 and a thyroidectomy in April, 1920. Her basal metabolic rate was plus 9 per cent in May, 1920, and minus 17 per cent in November, 1921.

Case 3 (fig. 1) had several x-ray treatments for toxic goiter ending December, 1921. In January, 1922, her basal metabolic rate was minus 6 per cent. A double oophorectomy was performed in September, 1924. There were no further determinations of metabolism until April, 1925, when her rate was minus 21 per cent.

Case 11 (see table 1) had x-ray treatment for toxic goiter ending September, 1922, when her basal metabolic rate was plus 11 per cent. The menopause occurred in May, 1925. No metabolism determinations were made until November, 1925, when her rate was minus 17 per cent.

In case 18 there was a tendency to a low metabolism before the oophorectomy was performed. In case 21 it is impossible to say

whether the oophorectomy had anything to do with the low rate. In cases 3 and 11 there is no record of the metabolism for about 3 years after x-ray treatment for thyrotoxicosis, so that it is not known whether it was low before the ovarian deficiency occurred. In short, in all these cases, one cannot preclude the possibility of a low metabolism which may have been present even before thyrotoxicosis occurred.

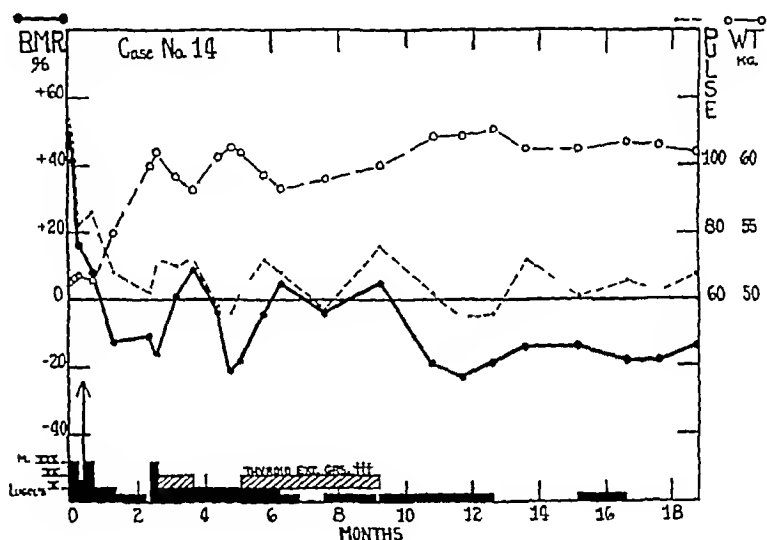


FIG 5 MRS A G, AGE 24 LAB No 3768 PERMANENT LOW METABOLISM FOLLOWING SUBTOTAL THYROIDECTOMY (ARROW) FOR EXOPHTHALMIC GOITER

No myxedema except mild temporary type during first 6 months after operation. The metabolism remained low after omission of iodine. Note well-marked rise in metabolism due to thyroid therapy, in contrast to the effect of thyroid shown in figure 1.

Influence of type of treatment employed for thyrotoxicosis

Permanent low metabolism without myxedema occurred spontaneously in 1 case after subtotal thyroidectomy in 13 cases after hemithyroidectomy in 2 cases after surgery and x-ray combined in 2 cases and after x-ray alone in 3 cases. Two patients (one treated by hemithyroidectomy and one by x-ray) had toxic adenoma, the remainder had exophthalmic goiter.

In 8 cases iodine was used at the time of subtotal thyroidectomy. In 5 of these 8 cases, although iodine was continued at intervals after operation, the data show that it was not the cause of their metabolic depression, as their metabolism remained low when iodine was omitted. In the other 3 instances (cases 15, 16 and 17, see table 1) iodine was continued practically throughout the period of the low metabolism. It is impossible to tell just what rôle this medication played in these instances until iodine is omitted for a sufficient length of time. They may be low rate cases of the temporary type (1), but are just as likely to be of the permanent type like case 14 (fig 5), case 1 (fig 2) and case 13 (table 1), in which the metabolism remained low after iodine was omitted.

It is evident that in the very great majority of instances of permanent low metabolism without myxedema, iodine therapy was not a factor which need be considered, in striking contrast to the important rôle it played in temporary low metabolism (1).

Permanent low metabolism without myxedema preceded by temporary low metabolism without myxedema Possible relationships between the two

Having now presented cases both of temporary low metabolism without myxedema (1) and of permanent low metabolism without myxedema, following thyrotoxicosis, it seems desirable to consider a case that may furnish a connecting link between the two, viz, one which shows both types of low metabolism. Such a case is no 18 listed in the paper on temporary low metabolism. Her chart is given here (see fig 6) because this seems to be the logical place for it. She had 3 x-ray treatments for exophthalmic goiter. One month later, without medication, her metabolism was minus 17 per cent. Thyrotoxicosis recurred, with a rate of plus 22 per cent. She had 2 more x-ray treatments, and one month later, without medication, her rate was minus 17 per cent again. There was no hypothyroidism either time. Her metabolism then rose without thyroid therapy to standard normal (ranging from minus 2 to minus 7 per cent) for a period of 14 months, during which time she displayed no clinical evidence of thyrotoxicosis. Her rate then dropped spontaneously to approximately its former low level, without any accompanying hy-

pothyroidism Thyroid extract, up to 3 grains daily, was prescribed This affected her metabolism very little and produced only very questionable clinical improvement On omission of this medication (for 7 months at the date of her last test) her rate was, with one exception, about minus 15 per cent She claimed that she felt just as well, if not better, than when on thyroid extract, and appeared to be a perfectly healthy individual

The significance of this case will be elaborated in the discussion

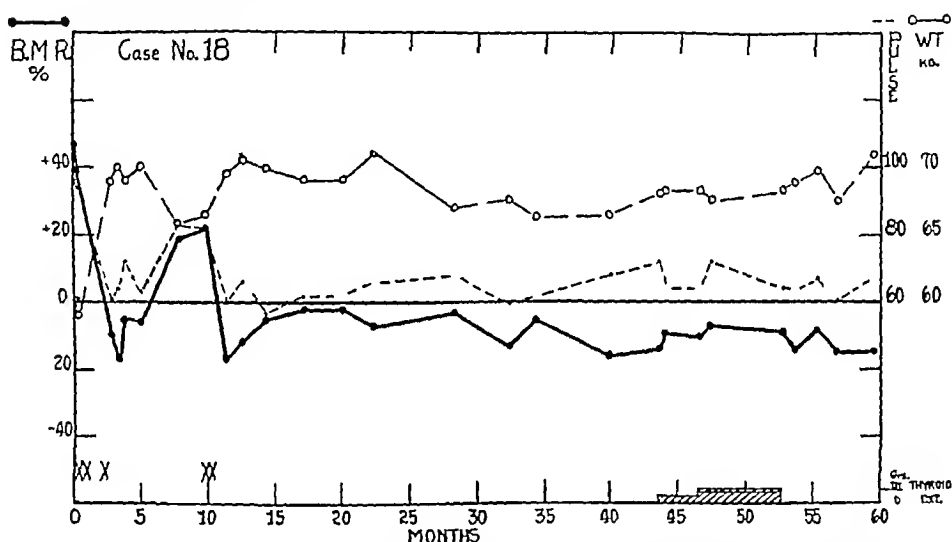


FIG 6 MISS L B, AGE 23 LAB No 1510 TEMPORARY LOW METABOLISM WITHOUT MYXEDEMA FOLLOWED BY PERMANENT LOW METABOLISM WITHOUT MYXEDEMA, OCCURRING AFTER X-RAY TREATMENT (X) FOR EXOPHTHALMIC GOITER

DISCUSSION

The fact that a permanent low basal metabolic rate may be normal for some individuals, does not seem to be very clearly recognized There are healthy people who have a metabolism as low as minus 16 to minus 25 per cent They look and feel perfectly well, and display no symptoms of hypothyroidism Sturgis (3) reports such a case with a rate of minus 22 to minus 25 per cent Wishart (4) reports 3 cases with rates of minus 16, minus 21 and minus 21 per cent respectively We have seen several such cases in our experience

They differ in no apparent respect from healthy people with a standard normal metabolic rate

Then again there are those individuals with a low metabolism who have symptoms such as headaches, dizziness, weakness, chronic fatigue and nervousness. In fact the nervousness is often so marked that they suggest mild hyperthyroidism rather than hypothyroidism. They do not *look* myxedematous in the least. The hair and skin are usually not dry. There is no edema. They are not slowed up. One of their chief complaints is that of feeling tired all the time. In this respect only, they suggest myxedema. In general, they present an entirely different picture. Were it not for their low metabolism and susceptibility to fatigue, thyroid extract would rarely be tried on them. There are many persons whose metabolism is within the standard normal zone of plus or minus 10 per cent who have the same complaints, yet because their metabolism is at this higher level and no definite clinical pathology is found, they are often regarded as more or less normal, or at most "neurotic." Certain observers have reported patients of this type, who have a low metabolism, as improved on thyroid therapy and have on this basis diagnosed the condition as a form of hypothyroidism, even though the symptoms are on the whole quite atypical of true thyroid deficiency. It seems much more likely that the explanation lies in some other obscure pathology about which nothing is known at present. The low metabolism often found may be an essential part of this picture. On the other hand, it may be "normal" for the particular individual, just as in the group of cases mentioned in the foregoing paragraph.

Coming now to permanent low metabolism *following thyrotoxicosis*, we know that in a certain proportion of cases it is associated with definite underfunction of the thyroid gland—true myxedema. In another much larger proportion of cases, however, there are no symptoms of myxedema. The patients are of the two types just described, the majority of them being of the first type, i.e., apparently normal individuals. Inasmuch as a surprising number of normal people who have never had thyrotoxicosis have a low metabolism, it is only reasonable to suppose that in a group of patients who develop toxic goiter, a certain number have normally a low metabolism which manifests itself as soon as the thyrotoxicosis disappears. In

fact Plummer (5) suggests that perhaps more cases of exophthalmic goiter are recruited from the group of persons with a low metabolism—many of whom are of the asthenic type—than from any other group. He actually has observed patients with a low basal metabolic rate who later developed exophthalmic goiter.

As previously stated, abnormalities other than myxedema that are at present known to be associated with a low metabolism, were not factors in our cases, with the exception of hypogonadism. The possibility of the influence of this factor must be considered in four cases already described. The knowledge of the effect of ovarian deficiency per se on metabolism is very ill defined, although the occurrence of myxedema about the time of the menopause is well known. King (6) from his own observations and DuBois (7) from a review of the literature, have come to the conclusion that loss of ovarian function has little effect on metabolic rate. Several others, notably Aub (8) and Bailey (9), have concluded, both from the literature and from their own observations, that experimental oophorectomy sometimes depresses the basal metabolism. In the instances where a low metabolism is found after removal of the ovaries or the occurrence of the menopause, the possibility of its having been present before the ovarian deficiency developed, and of its representing the normal metabolic level of the patient, never seems to be taken into consideration. Inasmuch as our four patients appeared to be healthy individuals, we feel that it is just as reasonable to assume that their low metabolism was "normal" for them as to assume that it was due to an ovarian deficiency.

In brief, it is suggested that permanent low metabolism without myxedema following toxic goiter may be a manifestation of any one of the following:

1. A return to a low metabolism which is normal for the individual and which was probably present before the development of thyrotoxicosis, the patients concerned being healthy persons.

2. A return to a low metabolism which was probably present before thyrotoxicosis developed and which may be "normal" for the individual, the patients concerned, however, having symptoms such as headaches, dizziness, susceptibility to fatigue, nervousness, etc.

3. Intervening abnormalities other than myxedema, that are known to be associated with low metabolism.

In group 1 thyroid therapy is a useless procedure, except as a therapeutic test to establish beyond doubt the type of patient with which one is dealing. When this is accomplished, it should be omitted. Otherwise the patient may continue taking thyroid extract unnecessarily for years, and even may be made quite uncomfortable at times from efforts to raise the metabolism to standard normal by giving large doses. In view of the possible benefit in group 2, thyroid therapy may be tried on these patients. It is difficult to believe, even in cases which may improve under such treatment, that the underlying pathology is primary under function of the thyroid. It should be stressed that in patients of this type sufficient thyroid to produce improvement often causes very little increase in metabolism. In group 3 the most effective treatment is that which is directed at the underlying cause of the patient's clinical symptoms. Thyroid therapy is not a routine procedure, but is said to be of value in certain rare instances, e g when used in large doses in order to reduce the edema of chronic nephrosis.

The idea is all too prevalent that when the metabolism is below accepted normal standards there must be a depressed function of the thyroid. Consequently when a situation arises where the circumstances are supposedly more propitious than usual for the occurrence of myxedema, viz, after a subtotal thyroidectomy or after several x ray treatments of the thyroid, such a diagnosis is doubly likely to be made, regardless of the clinical picture. This is as reasonable as saying that because the blood pressure is high, the patient must have chronic nephritis. We should not stress this point were it not for the fact that wrong diagnoses are so common, evidently due to the implicit belief that there is a practically perfect correlation between myxedema and low metabolism. This is the result of thinking of the normal in terms of averages and not taking individual variations sufficiently into account. The need for broadening our ideas of what is normal, to allow for occasional variations, applies to many other phases of medicine besides basal metabolism.

Those who report benefit from thyroid therapy in low rate cases without myxedema, mention that in some instances they were not successful. Our experience in this clinic has been that most of our low rate cases without myxedema have received no benefit from

thyroid medication. One or two have had headaches relieved. A few others thought they felt brighter and a little more energetic at first, although several months after omission of thyroid many of them felt just as well as ever and had no desire to resume the tablets.

The explanations offered for the lack of effect in these instances indicate the current attitude toward the status of the patient. The inference is made that it is due to such various causes as the long-standing nature of the symptoms, with complicating arteriosclerosis (10), lack of absorption from the gastro-intestinal tract (3), loss of potency of the thyroid preparation (3), or insufficiency of dosage (11). Practically no consideration is given to possible biological differences in patients themselves. Several of our cases in which thyroid had no clinical effect were young people who did not have any arteriosclerotic changes. In many others we are sure that potency, absorption and dosage were not at fault, because the metabolism rose to standard normal, whether with varying doses of thyroid extract by mouth or with intravenous thyroxin—yet there was no improvement clinically. That is to say, we got metabolic but not clinical results. In some instances where we did not get even a significant effect on metabolism, we are sure that the thyroid extract was absorbed, because symptoms of thyroid intoxication supervened whenever the dose was increased beyond the patient's tolerance. For example, case 3 (fig 1) with a metabolism of about minus 23 per cent, suffered from precordial pain and palpitation whenever her dose was increased to 6 grains daily in spite of the fact that her rate remained practically unaffected, i.e., she developed some symptoms of thyroid intoxication with a distinctly subnormal rate. A case dealt with in the paper on myxedema following thyrotoxicosis (2) is somewhat similar in this respect. He developed myxedema a few months after a subtotal thyroidectomy in 1918. Thyroid has never been omitted long enough in the subsequent 9 years to observe whether he still has thyroid deficiency. It would seem at present that, regardless of myxedema, he has normally a low rate in the neighborhood of minus 15 to minus 25 per cent, because he felt perfectly well and his metabolism remained within this range although he was on 6 grains of thyroid daily. This is more than sufficient to raise the metabolism to normal in most cases of myxedema. In fact many show symptoms of thyroid intoxication on

this dose When he took the large dose of 12 grains daily, his rate rose to minus 2 per cent, but he experienced severe precordial pain and palpitation which disappeared promptly on omission of thyroid, i e , sufficient thyroid to make his metabolism standard normal produced symptoms of thyroid intoxication

In general, patients with low metabolism and no myxedema may be divided into two groups with respect to the effect of thyroid extract by mouth on metabolic rate

1 Those who respond readily to moderate doses with a well-marked rise in metabolism, e g , case 14 (fig 5)

2 Those who require large doses to affect the metabolism perceptibly Moderate doses do not produce any very significant change, e g , case 3 (fig 1)

The latter type is fairly common, and in this group, symptoms of thyroid intoxication may supervene with a definitely sub normal rate As a general rule, the patient who requires more than 4 grains of thyroid daily to raise the metabolism to standard normal has either not got myxedema, or else if he has that deficiency, has in addition a low rate normally The maintenance dose for most cases of true myxedema seen in this clinic is $1\frac{1}{2}$ to 3 grains of thyroid extract (Armour's) daily

Treating the metabolism rather than the clinical symptoms appears to be a prevalent practice The folly of flooding the body with an excess of a normal product is obvious, and it is very poor therapy

Since several of our cases of temporary low metabolism without myxedema (1) seem to be best accounted for by the same hypothesis that we have elaborated above for our cases of permanent low metabolism without myxedema, it seems important to consider any possible relationship that may exist between the two If both types of low metabolism represent depressions to a metabolic level which is normal for the individual, the logical conclusion is that several of the patients who had temporary low metabolism without myxedema may eventually develop permanent low metabolism without myxedema Case 18 from study I (fig 6 in this study) thus may be regarded as a connecting link between these two types of low metabolism In such an instance the intervening period of standard normal metabolism evidently represents a period of mild thyrotoxicosis

These considerations lead up to a fairly important deduction, which is supported by actual observation, viz, that thyrotoxicosis may exist with a standard normal metabolism. This accounts satisfactorily for the repeated depressions of the metabolism from a standard normal to a low level produced by iodine months to years after operation, coincident with the disappearance of signs and symptoms either diagnostic of, or suggestive of, mild thyrotoxicosis (1).

It follows that in order to judge the true elevation of the metabolic rate of patients who develop thyrotoxicosis, it is necessary to know their normal metabolic level. The clinical significance of this point may be illustrated by referring to case 8 (table 1). When first seen, this patient had definite signs and symptoms of thyrotoxicosis with a rate of plus 10 per cent, but because her metabolism was standard normal, she was given no treatment. In view of her low rates of minus 28 and minus 14 per cent, 2 and 3 years respectively after operation, when she was not receiving any medication and was in perfectly good health, her level of plus 10 per cent in 1920 was probably equivalent to plus 24 or plus 38 per cent in a person with a normal level of about zero.

SUMMARY

Twenty-one cases have been presented showing permanent low metabolism without myxedema, following recovery from thyrotoxicosis.

After recovery, the patients were for the most part apparently normal individuals.

In the cases in which thyroid therapy was tried, no definite beneficial effect was noted clinically, although potency, absorption and dosage of the drug were not at fault.

Many of these patients required much more thyroid extract to raise the basal metabolism to standard normal than do patients with spontaneous myxedema. Moreover, symptoms of thyroid intoxication due to thyroid feeding sometimes occurred while the metabolism was still low.

The importance of treating the patient rather than the basal metabolic rate has been stressed.

CONCLUSIONS

Facts are cited which are consistent with the hypothesis that permanent low metabolism without myxedema following thyrotoxicosis, is, in most instances, a return to a normal metabolic level, which was probably low even before the development of the disease

Thyrotoxicosis may exist with a standard normal basal metabolic rate

The interpretation of the degree of basal metabolic elevation in thyrotoxicosis is directly affected by the level of the patient's normal metabolism

Temporary low metabolism without myxedema may be, in some instances, an initial phase in the eventual development of permanent low metabolism without myxedema

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A NOTE ON THE INFLUENCE OF THE CIRCULATION ON THE UTILIZATION OF CARBOHYDRATES¹

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In a recent paper published in this JOURNAL, Lennox and Bellinger (1) have presented the results of an extensive study of the blood sugar curves of non-diabetic individuals, following the repeated oral and intravenous administration of glucose. They find that in the majority of their subjects the blood sugar curve was higher at the initial trial than it was 1 to 312 days later, after sugar administration had been repeated. In view of these findings Lennox suggests that he is "loathe to conclude that a lowered second curve is necessarily due to treatment or to experimental procedure." He suggests that the lowering of the height of the second curve is to be ascribed to the influence of the first ingestion of glucose.

Prominent among the work cited is that of Cajori, Crouter and Pemberton (2) on the effect of changes in the circulation on carbohydrate utilization. The purpose of the present communication is to show that Lennox's criticism of the interpretation of repeated blood sugar curves does not apply to the above mentioned work of the present writers.

Cajori, Crouter, and Pemberton (2) found that an exaggerated and prolonged hyperglycemia following the ingestion of glucose could be induced in a certain proportion of patients with chronic arthritis by interference with the blood supply to large muscle masses through elevation of the legs. The results of these experiments seemed of considerable significance in that they offered, with other evidence, an explanation of certain of the pathological changes in arthritis, and, of the delayed sugar removal from the blood ("lowered sugar tolerance")

¹ The work here reported is part of a study on chronic arthritis in collaboration with R B Osgood, M D of Boston. The expenses were defrayed by contributions from various sources including a number of patients.

so frequently encountered in arthritis (3) These experiments also indicated that the character of the blood supply to tissues active in sugar removal is an important factor in the early utilization of carbohydrates The importance of these conclusions was such that it seemed advisable to repeat the experiments and extend the series of cases studied This was done and similar results were obtained, 50 per cent of those arthritics in whom a delayed sugar removal was not always present showed a higher blood sugar curve when the legs were elevated

In the first series of these experiments, with one exception, the initial blood sugar curve was obtained when the subjects had their legs elevated, as Lennox has pointed out According to him, the lower curve, subsequently found, may have been the result of a "natural" tendency, following glucose ingestion, for a second blood sugar curve to be lower than the first In the second series, however (12 experiments) the first blood sugar curve, with two exceptions, was determined when the subject was seated, and the second when the legs were elevated As has been mentioned above, results were obtained with essentially the same correlation between the position of the subject and height of blood sugar curve as in the first series, though the order of the experiment was reversed and the high blood sugar curve was observed on the second trial This reversal of procedure in the two series was unpremeditated as we were at that time unfamiliar with Lennox's conclusions We were interested in the response to the change in posture manifested by those arthritics (40 per cent) who ordinarily showed no delay in blood sugar removal, we endeavored to choose such types for the rather arduous experiment dealing with posture We did not publish the details of this second series of experiments, contenting ourselves with the statement that the data were entirely confirmatory of the first series (4) These results now have added significance in that they are not open to the objections raised by Lennox in his recent article

In 10 of the 12 experiments of the series here published, the first blood sugar curve was determined when the subject was seated, the second curve was determined when the subject was recumbent with legs elevated Five, or 50 per cent of the 10 subjects had a higher blood sugar curve when the legs were elevated In our first series,

Effect of posture on the blood sugar curve following glucose ingestion

Subject	Seated			Legs elevated			Days between tests
	Date	Time	Blood sugar	Date	Time	Blood sugar	
	1925 1926	minutes	mgm. per 100 cc	1926	minutes	mgm. per 100 cc	
1	December 31	0	94	January 4	0		4
		30	135		27	132	
		60	92		60	99	
2	January 5	0	90	January 19	0		14
		32	116		35	108	
		67	130		65	155	
3	January 13	0	103	January 15	0		2
		30	132		33	135	
		60	115		65	127	
4	January 18	0	99	January 22	0		4
		40	122		32	118	
		65	128		60	110	
5	January 22	0		January 20	0		2
		35	166		30	123	
		65	140		60	174	
6	February 1	0	104	February 3	0		2
		40	125		30	148	
		70	111		60	167	
7	February 15	0	104	February 17	0		2
		30	152		30	168	
		65	120		60	146	
8	March 3	0	99	March 10	0		7
		30	124		30	159	
		60	109		60	121	
9	March 10	0	99	March 18	0		8
		30	142		30	152	
		65	122		60	146	
10*	March 19	0	97	March 25	0		6
		30	151		40	129	
		60	119		70	110	
11	March 29	0	94	April 2	0		4
		30	156		35	153	
		60	112		65	118	
12*	April 24	0		April 17	0	98	7
		30	157		30	177	
		60	175		62	189	

* Normal individual

previously published, the first curve was determined, in 12 of the 13 experiments, with the subject's legs elevated and the second curve was determined with the subjects seated. Seven, or 58 per cent, of the 12 subjects showed a higher curve when the legs were elevated. The details of the second series are presented in table 1.

Lennox's suggestion that the lowered blood sugar curve, obtained when glucose is administered a second time results from the stimulating effect of the initial dose of glucose, is deserving of comment. Since the work of Foster (5), appreciation is general that glucose is a powerful stimulant to the sugar-disposing mechanism and that a much less pronounced hyperglycemia results from massive glucose ingestion if the mechanism which removes excess sugar from the blood has been previously stimulated by glucose administration. Reinhold and Karr (6) have shown that other sugars are effective, through previous feeding, in reducing the hyperglycemia resulting from glucose ingestion. Du Vigneard and Karr (7) and also Greenwald and his co-workers (8) have shown that proteins as well as carbohydrates stimulate the sugar-disposing mechanism, whereas following fat feeding an exaggerated hyperglycemia results after glucose administration, a situation which also prevails during fasting. How long the stimulating effect of glucose or other foods persists upon the mechanism that removes sugar from the blood has not been determined. The interval between successive tests in our two series varied, with two exceptions, from 2 to 14 days. In 6 of the 31 subjects of Lennox and Bellinger whose second blood sugar curve was lower than the initial curve, the interval between successive tests was similar to the interval in our experiments. In the others it was longer. In a number, the period between tests was 300 to 200 days (1, table 2, p. 335).

It does not seem probable that the stimulus of a dose of glucose should endure for 14 days, not to say many months, without being considerably modified, if not completely abolished, by the changing metabolic conditions incident to ordinary food ingestion.

The influence on the blood sugar curve of the state of nutrition (starvation, certain diets), together with the effect of previous food ingestion, has for some time been known. It would seem, nevertheless, that duplicate curves determined at intervals of a few days are

TABLE 2
Blood sugar curves of arthritics, remaining persistently high

Subject	Date	Time	Blood sugar	Date	Time	Blood sugar	Days between tests
	1918	minutes	mgm. per 100 cc.	1918	minutes	mgm. per 100 cc.	
Robbins*	November 29	0	125	December 23	0	142	24
		60	188		60	185	
		120	167		120	140	
		180	107		180	134	
Hayes*	December 11	0	136	1919 February 17	0	132	68
		60	178		30	201	
		120	121		60	250	
		180	79		120	173	
Martin	December 26	0	120	March 5	0	106	69
		15	125		30	198	
		30	175		60	186	
		45	155		120	185	
Massood	December 31	0	203	January 6	0	144	6
		60	262		30	168	
		120	212		60	220	
		180	167		120	188	
Lowe	1919 January 13	0	146	May 11	0	108	118
		30	250		30	200	
		60	177		60	167	
		120	130				
Wittington	January 31	0	127	February 4	0	130	4
		30	182		30	178	
		60	144		60	131	
		120	119		120	115	
Cullen	February 12	0	101	February 17	0	147	5
		30	182		30	174	
		60	136		60	161	
		120	140		120	132	
Oberg	January 31	0	112	February 4	0	114	4
		30	200		30	238	
		60	165		60	214	
		120	121		120	206	
		180	114		180	67	

* Sugar determinations on plasma.

indicative of conditions, experimental or otherwise that occur during the interval, affecting the ability of the body to remove from the blood excessive amounts of ingested glucose. At all events, any possible influence from a previous "sugar tolerance test" can be eliminated from discussion when considering the induction of a delayed sugar removal following interference with the circulation in the limbs. The experiments definitely indicate that a relative "anemia" of the muscular tissues at least constitutes a part of the pathological picture in arthritis and probably is one cause of the delayed sugar removal, of non-diabetic nature, seen in arthritis.

In this connection, attention should be called to that group of arthritics whose blood sugar curves remain persistently high. Lennox and Bellinger report similar findings in a minority of other types of subjects. Previous observations by Pemberton and Foster (9), published only in part, herewith recorded in table 2, show in a series of persons, some of whom were active arthritics, some convalescent and some symptomatically cured, that the second blood sugar curve was sometimes even higher than the first, notwithstanding previous ingestion of glucose at various intervals before the second test. Granting that the ingestion of sugar does influence subsequent carbohydrate utilization, it is plain that this influence may be greatly overshadowed by other factors and that, furthermore, in the cases cited, there is no evidence of any such influence from the previously injected glucose.

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GASTRIC FUNCTION IN CASES OF GASTRIC AND DUODENAL ULCER

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Although the association of high gastric acidity with certain cases of gastric and duodenal ulcer has long been recognized, the question of whether there are any findings on gastric analysis constant enough to be of real diagnostic value has never been settled. The figures in the literature cover a wide range, in most series of ulcer cases hyperacidity is said to have been present in 30 to 70 per cent of the patients, whereas the remainder showed normal or subacidity. Palmer (1) has recently reviewed the question of anacidity with gastric ulcer. Some writers would relate the tendency to hyperacidity with position of the ulcer near the pylorus or with other factors. Hurst (2) is impressed by the occurrence of duodenal ulcer only in people who already have a hyperacidity. Brown (3) has recently summarized the question as follows: "Somewhat less than 50 per cent of patients show high normal or hyperacid conditions. In rather more than 50 per cent of cases the figures are well within normal limits, occasionally subacidity occurs and rarely anacidity."

In regard to the volume of secretion even less definite information is available. The presence of large volumes has been assumed in certain instances of ulcer but the absence of methods for volume determinations has made any accurate comparisons with the normal impossible.

In summary, then, the general implication of the literature is to the effect that no constant or characteristic findings on gastric analysis are associated with peptic ulcer.

In a series of recent papers, Bloomfield and Keefer (4) draw attention to the inadequacy of the current methods of studying gastric function by means of the ordinary fractional test. Using a new procedure which made it possible to estimate, under uniform conditions

TABLE I
Clinical data of ulcer cases

Case number	Sex	Age	Diagnosis	Operation	Melena or haematemesis	X ray	Remarks
1	M	30	Gastric ulcer		Yes	Definite crater	Lesser curvature
2	M	30	Gastric ulcer		Yes	Definite crater	Near pylorus
3	M	33	Gastric ulcer			Large penetrating ulcer	Lesser curvature
4	M	39	Gastric ulcer		Yes	Definite crater	Lesser curvature
5	M	48	Gastric ulcer	Large chronic ulcer at pylorus		Lesion at pylorus with obstruction	<i>Pyloric obstruction</i>
6	M	49	Gastric ulcer	Large chronic ulcer lesser curvature			Lesser curvature
7	M	53	Gastric ulcer	Old callous ulcer at pylorus		Pyloric obstruction	<i>Pyloric obstruction</i>
8	M	55	Gastric ulcer	Chronic perforating ulcer lesser curvature		Definite crater	Lesser curvature
9	M	56	Gastric ulcer		Yes	Filling defect lesser curvature	Lesser curvature
10	M	60	Gastric ulcer	Large callous ulcer lesser curvature	Yes	Crater on lesser curvature	Lesser curvature
11	M	61	Gastric ulcer	Huge old ulcer near pylorus	Yes		Near pylorus but no marked obstruction
12	M	62	Gastric ulcer	Large ulcer on lesser curvature near pylorus	Yes	Annular defect at pylorus without obstruction	Lesser curvature near pylorus
13	M	69	Gastric ulcer	Large ulcer lesser curvature		Definite crater	Lesser curvature
14	M	69	Gastric ulcer	Large ulcer at pylorus		Ulcerative lesion at pylorus with obstruction	<i>Pyloric obstruction</i>
15	F	35	Gastric ulcer		Yes	Filling defect lesser curvature	Lesser curvature
16	F	39	Gastric ulcer	Penetrating ulcer lesser curvature	Yes	Crater	Lesser curvature

		Ulcer near pylorus				Diagnosis at autopsy	
		Gastric ulcer	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
17	F	66	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
18	M.	27	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
19	M	28	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
20	M	29	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
21	M	30	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
22	M	30	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
23	M.	33	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
24	M	36	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
25	M.	36	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
26	M	38	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
27	M	38	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
28	M	38	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
29	M.	39	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
30	M	39	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
31	M	39	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
32	M	41	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
33	M	45	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
		Large ulcer 2 cm. beyond pylorus		Yes	Filling defect of duodenum	Typical history	
34	M	46	Duodenal ulcer	Yes	Filling defect of duodenum	Typical history	
35	M	60	Duodenal ulcer	Yes	Filling defect of duodenum	Typical history	
		Large ulcer just beyond pylorus		Yes	Filling defect in duodenum	Typical history	
36	F	43	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	
37	F	49	Duodenal ulcer	Yes	Filling defect in duodenum	Typical history	

and with reasonable accuracy, the acidity of the undiluted gastric juice, the volume of secretion and the emptying time, after a standard stimulus (50 cc of 7 per cent alcohol), they determined the normal variations and, in general, set standards with which the findings in instances of gastric disease might be compared. Application of these methods in a few cases of peptic ulcer (5) revealed a distinct group of findings and served as a stimulus for further observations. The present report deals with gastric functional studies in a larger series of cases of gastric and duodenal ulcer.

MATERIAL

Thirty-seven consecutive instances of peptic ulcer were studied. It seemed essential to include no questionable cases. The diagnosis was confirmed either by operation or by unequivocal x-ray evidence together with bleeding. In every case the diagnosis was made and the patient was accepted for the series before the gastric analysis was done in order that the latter might play no part in influencing our opinion. The main facts of clinical importance are summarized in table 1.

METHODS

Studies of gastric function were carried out by the method which has been previously described in detail (6). The curve of acidity, the volume of secretion, the gastric volume curve and the emptying time were determined following the standard alcohol stimulus.

RESULTS

Acidity The heavy line in chart 1 shows the average acidity of the gastric juice at various age periods in a control group without organic disease of the stomach. It has already been pointed out (4) that acidity on the whole diminishes with advancing years, and in considering the findings in disease this fact must be taken into account. Each dot in chart 1 indicates the highest acidity of the pure juice after the alcohol stimulus in a different case of peptic ulcer, plotted in relation to the age of the patient. That the acidity in every instance but one was above the average is strikingly shown and the line of average acidity in the ulcer cases (broken line) brings this fact out even more

clearly. There seems to be little question but that when the acidity of the pure juice is determined, with elimination of the factors of dilution by test meal and neutralization by the buffers of saliva and test meal, high values are found to be present with great uniformity. In one case, (no 14) there was absence of free hydrochloric acid and the

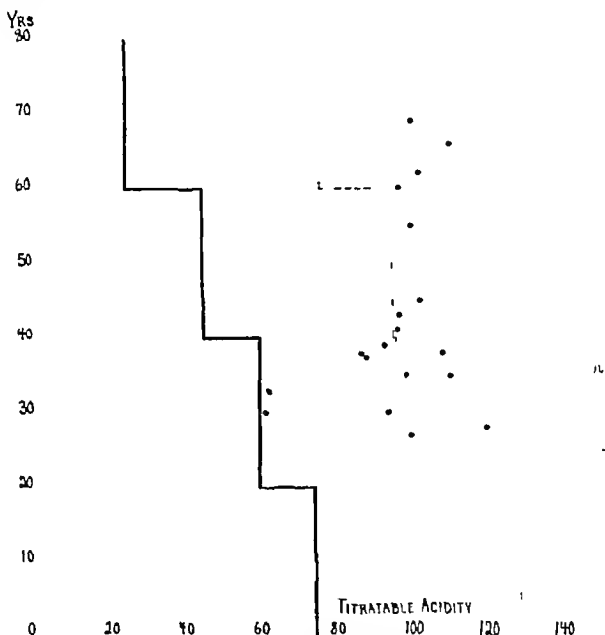


CHART 1 RELATION OF ACIDITY TO AGE IN ULCER CASES

pH of the gastric juice (colorimetric method) was found to be above 6.0. A simple gastric ulcer was found at operation, and autopsy later confirmed the diagnosis. No striking changes were discovered in the mucous membrane of the stomach. A note on this patient has been published (7).

Volume of secretion In chart 2 each dot represents the maximum ten-minute volume of gastric secretion following the standard alcohol stimulus, plotted in relation to the age of the patient. The heavy black line indicates the average ten-minute volume of secretion of the controls in various age periods. Here again one sees that in practically every case the volume of secretion in people with peptic ulcer is above the normal average.

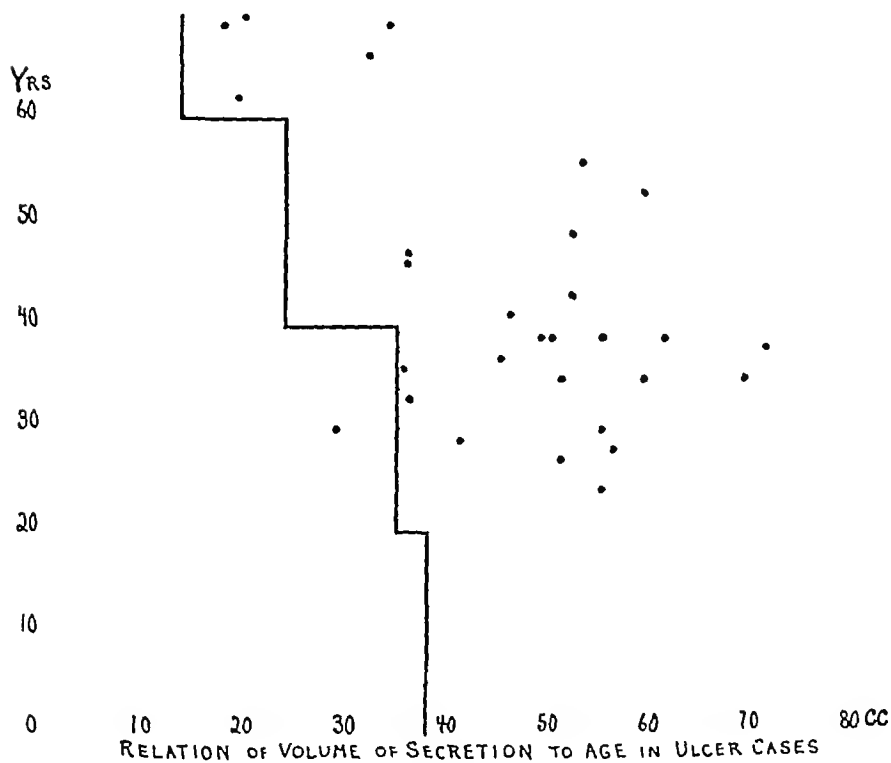


CHART 2

Motility Various disorders of gastric motility have been described in connection with peptic ulcer. Actual pyloric stenosis, when marked, constitutes, of course, a definite clinical entity with distinctive features. To what extent the motility is disturbed by ulcer which has not led to pyloric occlusion is less clear. The present observations are based on complete aspirations of the entire gastric contents at ten-minute intervals after introduction of the 50 cc alcohol meal.

A 10 cc. sample is retained and the remainder is immediately returned to the stomach. This procedure makes possible the plotting of curves

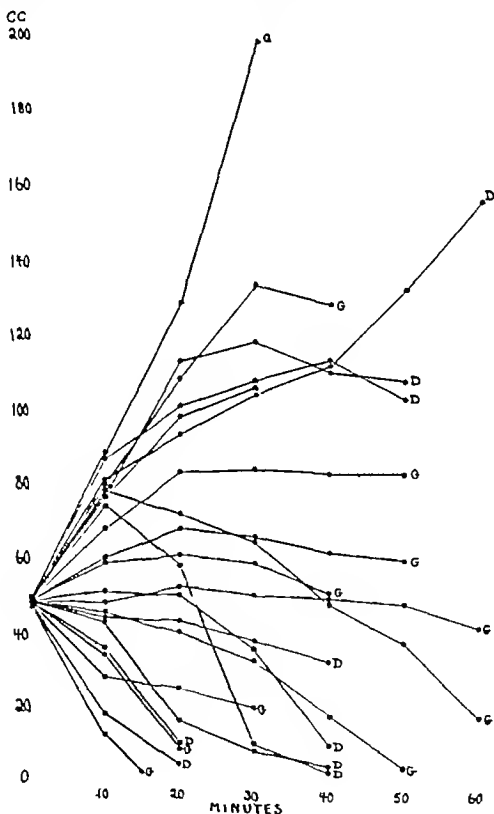


CHART 3 VOLUME CURVES IN ULCER CASES

of gastric volume, a series from a group of control cases has already been published (4) In chart 3 are shown such curves from cases of

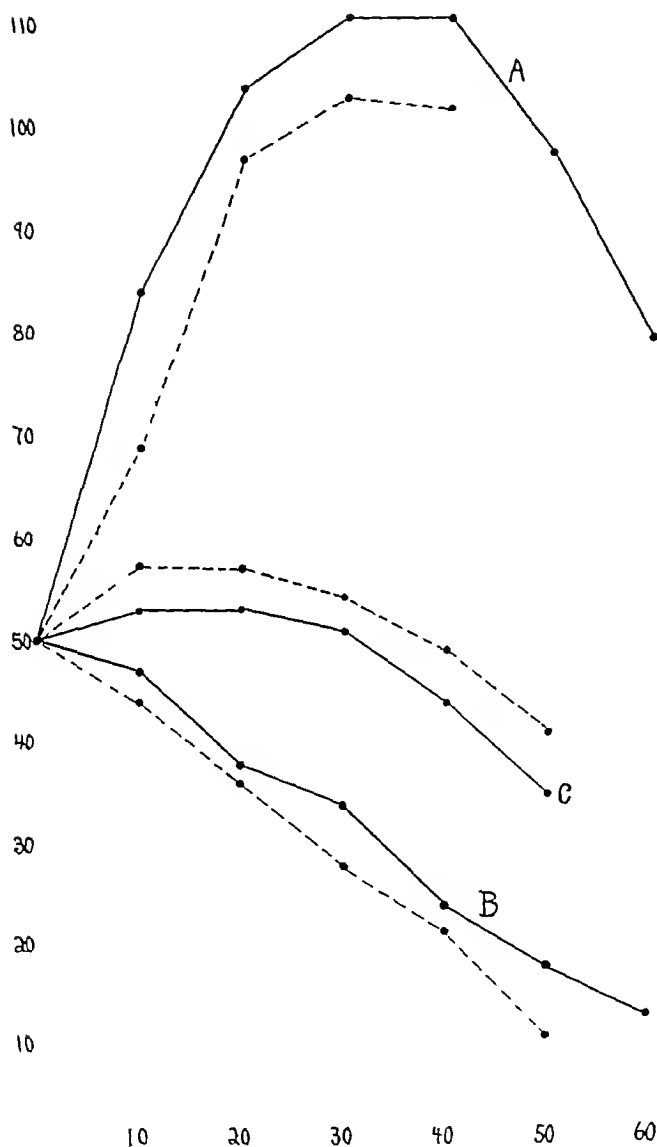


CHART 4 COMPOSITE VOLUME CURVES

peptic ulcer As in the control group several types are manifest there may be an initial rise later followed by emptying, the volume may immediately decrease, or there may be an intermediate type of

curve In chart 4 the solid lines represent composite graphs of the volume curves in the controls without disease of the stomach curve C of all the cases, curve A of all cases showing an initial rise and curve B of all cases showing an initial fall The dotted lines represent similar composite graphs of the curves shown in chart 3 It appears that motility in peptic ulcer cases as revealed by the present methods is practically identical with motility in the control group

COMPARISON OF FINDINGS IN GASTRIC AND DUODENAL ULCER

On referring to table 1 one is struck by the fact that the gastric ulcer patients on the whole were older than those with duodenal ulcer The age of the former averaged 57 years, of the latter 38 years The same general conditions, however, as regards acidity and volume of secretion held in the two groups The average acidity in the gastric ulcer cases was 90, in the duodenal ulcer cases 99, the average ten-minute secretory volume in the former was 46.5 cc., in the latter 43.0 cc The series is not large enough to justify conclusions as to differences of motility in the two groups However, reference to chart 3 shows that every type of volume curve was obtained both in gastric and duodenal ulcer cases

DISCUSSION

The purpose of the present work has been to make an objective comparison of gastric function using a standard method in a series of verified instances of gastric and duodenal ulcer and in a control group It appears that ulcer cases with one exception showed higher acidity and larger volumes of gastric juice than the average figures for the controls in the various age periods Motility on the whole showed no special features in the ulcer cases

Throughout this work we have kept in mind the question of the practical diagnostic value of these findings It has already been shown that great variations exist in the gastric findings in people without organic disease of the stomach The mere presence of high acidity and large volume of secretion is therefore not *prima facie* evidence of ulcer Whether people with this type of gastric activity are especially susceptible to ulcer as Hurst (2) suggests, will be discussed in a future communication The *absence* of high acidity and

large volume, on the other hand, we believe to be of the utmost importance in ruling out the presence of benign ulcer. In cases of indigestion, for example, with doubtful radiological signs, absence of high values for acidity and volume are very strong evidence against ulcer. The question of whether the high acidity is antecedent or consequent to the ulcer and the entire matter of the etiology of peptic ulcer are now under investigation and will be discussed in another paper.

CONCLUSIONS

1 Study of gastric function by a standard method shows that in verified cases of gastric and duodenal ulcer gastric acidity and volume of gastric secretion are greater than in people without gastric disease. These findings, with one exception, were uniform in a series of 37 cases.

2 No special characteristics of gastric motility in ulcer cases were discovered.

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THE INFLUENCE OF A DIET, HIGH IN BUTTER FAT, ON GROWTH, BLOOD FORMATION AND BLOOD DESTRUCTION

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The conception that a diet high in fat in some way influences blood formation and blood destruction, especially in pernicious anemia and in the anemias of infants, has been voiced repeatedly, and it has been recently restated by Minot and Murphy (1). The uncertainty, however, as to the effect of fat on the blood and blood forming organs is well illustrated in the literature. Minot and Murphy (1) empirically exclude most fat from the diet of pernicious anemia patients, while Koessler and associates (2) recommend a diet for the same disease in which approximately two thirds of the caloric intake is in form of fat, mainly derived from dairy products.

The theory that the blood forming organs are harmfully affected by excess fat and fatty acids derived especially from milk and its products is, in a measure, supported by the prevalence of pernicious anemia in countries where the dairy industry and consequent consumption of dairy products occupy a prominent place. Moreover, pernicious anemia patients are usually well nourished in contrast to those suffering from other diseases associated with anemia and histories of these patients show in many instances a choice of food rich in fat (1). Gibson and Howard (3) state that patients with pernicious anemia do not do well when butter is added to their diet. Hammarsten (4) points out that fat people as a rule tend to have less hemoglobin than thin people. Czerny (5a) claims that injurious agents present in milk produce anemia in infants. These agents are said to be fatty acids which cause an increase of blood destruction (6). As proof for this is cited the improvement which takes place as soon as milk is limited and other food products substituted. Stoeltzner (7) pointed out that a severe hemolytic anemia could be produced in children by goat's

milk This anemia disappeared as soon as the milk was eliminated Whether, however, all these anemias of infants are due to excess fat may be questioned Milk is very low in iron (8) and experimental anemias may be produced by milk diet and cured by the addition of iron (9) (10) It is also claimed that a vitamin deficiency may account for the anemia of infants fed exclusively on milk (11)

This paper deals with the effect of a high fat diet on the blood and blood-forming organs of the rat, and the evidence tends to show that if all the other necessary constituents of the diet are present, an excess of fat derived from milk exclusively does not of itself impede either growth or blood formation

EXPERIMENTAL

Sixteen healthy rats were used Of these eight were put on the stock diet of the laboratory to which was added milk, butter, bread, meat, celery and carrots, thus insuring a thoroughly mixed diet The remaining eight were fed a high fat diet in which 86.5 per cent of the caloric intake was derived from butter fat (See table 1) The protein was supplied by pure casein, and the salt mixture was the one recommended by Osborne and Mendel (12a) The creamery butter was washed repeatedly to free it from any salts, then cooled to low temperature and the water removed carefully The dry ingredients of the diet were thoroughly mixed after weighing, and then gradually worked into the butter to insure a complete mixture Two kilograms of the mixture were made at a time and the food was kept in the ice box between feedings The consistency of the mixture was such that no scattering of the food was possible, thus insuring fairly accurate measure of the quantities consumed To this diet was added a small piece of carrot or celery twice a week to provide some bulk and any possible constituent necessary for maintenance and growth as it was desirable to exclude as far as possible all factors influencing growth unfavorably except, potentially, the fat This very small amount of vegetables has been disregarded in calculations of the diets The food of the group on the high fat diet was carefully weighed during the whole of eight months and at no time were the dishes allowed to be empty All the rats were kept in individual wire cages with raised bottoms, and fresh water was supplied freely Examinations of

freely flowing blood from the tip of the tail were done twice a month. At the end of the experiment Zenker fixed tissues, stained with eosin and methylene blue, and for iron with the potassium ferri-cyanide method, were studied.

Each group of animals included (a) young rats, born in the laboratory and put on the diet at the age of 6 to 7 weeks, (b) mature animals about 24 months old.

The growth of the young animals proceeded at a rapid rate. The initial weight (see table 2) of four of them on high fat diet was doubled respectively in 86 (no 39), 69 (no 62), 47 (no 61), and 44 (no 37) days. The controls doubled their weight in 63, 56, 42 and 41 days. Most of the animals weighed over 100 grams before they were put on the

TABLE 1
Composition of high fat diet

	Weight, per cent	Calories in 1000 grams	Per cent of calories
Casein	20	820	10.7
Salt free washed butter	71	6,603	86.5
Fleishman's dried yeast	5	205*	2.6
Salt	4		

* The caloric value of Fleishman's yeast has been arbitrarily chosen as 4.1 calories per gram.

diet. The periods for doubling the weight are therefore longer than those reported by other observers as, for example, Hopkins (13) who found that starting with an initial weight of about 50 grams, the males (76 per cent) doubled their weight in 2 weeks, while females as a rule gained more slowly and irregularly.

All the animals of adult size on the high fat diet maintained and added to their weight (table 2). Toward the end of the experiment, however, they had dry, thin fur, and one of them a scab-like eruption on the neck. As slight dryness of the hair was also observed in one of the young animals on the high fat diet and in none of the controls, it may have some significance, in relation to the diet, worthy of investigation. The same phenomenon was observed by Frank (14) in his series of rats fed on high fat diet and he suggests that it may be due to the excess or disproportion of vitamin A in comparison with the

other vitamins. He found that feeding carrots from the beginning prevented the skin affection, and adding carrots to the diet after the eruption had appeared caused improvement. He also quotes Czerny (5b), who observed that tuberculous children fed 80 grams of cod

TABLE 2

Number	Red blood cells		Hemoglobin		White blood cells—average during period	Initial weight	Final weight	Gain of weight
	Average during period	Final	Average during period	Final				
High fat Growing rats								
	<i>millions</i>	<i>millions</i>	<i>per cent</i>	<i>per cent</i>	<i>thousands</i>	<i>grams</i>	<i>grams</i>	<i>grams</i>
39 ♀	8 6	8 3	76	88	12 3	102	262	160
37 ♂	9 8	10 3	80	83	11 1	84	368	284
61 ♂	9 8	9 9	87	99	9 3	136	443	307
62 ♂	9 7	10 0	81	83	7 0	139	424	285
Controls								
65 ♀	9 0	9 9	82	104	16 7	120	279	159
63 ♂	10 0	11 1	87	111	10 4	134	477	343
64 ♂	9 9	11 4	87	104	10 2	136	480	344
66 ♂	10 3	10 6	85	111	10 6	135	450	315
High fat. Adult rats								
18 ♀	8 4	9 5	80	76	10 7	244	277	33
19 ♀	8 5	9 1	83	77	19 2	284	315	31
20 ♀	8 9	8 5	77	70	15 3	262	286	24
21 ♀	9 1	9 3	88	80	16 3	261	317	56
Controls								
34 ♀	9 0	9 2	79	73	13 9	234	284	50
35 ♀	9 3	9 7	89	88	11 4	257	315	58

liver oil daily developed eczema which disappeared as soon as the cod liver oil was withdrawn.

The daily food consumption per 100 grams of live weight, calculated for the entire eight month period, varied from 3.26 to 3.55 grams for the adult group, and from 3.35 to 4.57 grams for the young rats. This,

expressed in calories, is from 24.9 to 27 calories for the adult group and from 25.6 to 34.7 for the young rats. The distribution of the caloric intake is illustrated in table 3. From the examination of this table it will be seen that for the two young rats put on the diet in April, the caloric intake per 100 grams live weight remained high for the first three months and then suddenly dropped in July. Numbers 61 and 62, put on the diet in the beginning of June, showed a high caloric intake and a gain of 108 and 88 grams respectively for the first month. There was a sudden drop in the caloric intake in July,

TABLE 3
Average caloric intake per day for 100 grams of live weight

Number	March	April	May	June	July	August	Septem- ber	Octo- ber	Novem- ber	Decem- ber	Janu- ary
High fat diet Growing rats											
37 ♂		59.2	42.8	40.9	24.2	25.2	27.9	24.0	21.5		
39 ♀		39.0	39.7	40.6	29.9	31.1	32.7	23.7	19.8		
61 ♂				51.9	28.2	28.4	22.9	25.2	16.2	19.6	18.6
62 ♂				53.0	29.1	31.4	29.1	28.3	18.0	22.1	20.3
High fat diet Adult rats											
18 ♀	34.0	27.9	25.8	27.9	23.7	23.6	24.8	22.1			
19 ♀	30.7	25.5	20.4	28.2	23.1	22.2	26.6	23.4			
20 ♀	36.4	27.9	23.7	31.6	26.1	23.1	24.1	26.0			
21 ♀	35.5	25.2	28.5	27.9	22.1	14.1	26.1	19.9			
Average	34.1	26.6	24.6	28.9	23.7	20.7	25.4	23.1			

then a gradual decline. In the adult rats, with very slight gain of weight, the caloric intake during the first month exceeded that in any of the others, and in July and especially August the consumption was low.

That the caloric requirements of the rat display a tendency to diminish with the increasing duration of the experiment has been shown by Macallum (15). One may add that the season also influences the consumption of food, the hot summer months showing a definite drop in the caloric intake, without, in these experiments, any tendency to loss of weight.

In table 2 the average red blood cell count during the entire period is recorded with the final count. In the young rats the final count as a rule is somewhat higher than the average, on account of the lower counts obtained during the period of growth. The same holds true of the hemoglobin. Although both the red blood cells and the hemoglobin are slightly lower in the animals fed on a high fat diet, they are well within normal limits as found in this laboratory in a series of 150 apparently healthy rats. The slightly lower hemoglobin may perhaps be due to a deficient intake of inorganic salts because of the high caloric diet. From the evidences at hand, however, there is no injurious effect on the blood-forming organs of the rat from an extremely high diet of milk fat.

In the adult rats the red blood cells stayed at approximately the same level throughout the experiment. The final hemoglobin tended to be lower in all the animals both in the high fat group and the controls. Possibly an age factor plays some rôle.

At necropsy nothing abnormal was noted in the animals on a high fat diet except excessive increase of abdominal fat. Microscopic examination of the bone marrow showed slight increase in fat cells but the blood forming constituents were entirely normal. The liver showed fatty infiltration in 6 out of 7 animals studied. This was marked in one case, moderate in two, and slight in three. In the eight controls two showed slight fatty infiltration of the liver.

Levine and Smith (16) in their experiments with high fat diet of shorter duration than the above found sections of the liver normal in structure and devoid of fat droplets.

DISCUSSION

That rats can grow on a diet in which the caloric intake of fat represents from 80 to 90 per cent of the total food has been shown by Osborne and Mendel (12b). They were able to secure growth in some of their rats and the failures were explained by the deficient intake of protein and salts due to the high caloric diet. Smith and Carey (17) were unable to secure growth in their rats at a normal rate after 50 days on a ration containing 86 per cent fat calories, derived from lard and cod liver oil, while Levine and Smith (16) feeding the same percentage of fat from the same sources secured normal, or slightly below

normal, growth from 30 to 180 grams in body weight. They concluded that rats grew as efficiently on a high fat diet as on a mixed diet and that the fat was utilized almost completely. Frank (14) feeding a ration of milk fat as high as 91 per cent of the caloric intake to rats found that the animals on the fat ration grew more rapidly than groups fed on a high carbohydrate diet or a normal diet.

The results of the experiments reported in this paper confirm those of the above authors, showing definitely that rats can grow to adult size and that adult rats can maintain and add to their weight over a period of eight months on a diet in which 86.5 per cent of the caloric intake is in the form of butter fat.

The relation of a high fat diet to blood formation and blood destruction has been deduced mainly from clinical observations. That a lack of fat in the diet and primarily perhaps a lack of the fat soluble vitamins will cause a rapid general decline accompanied by anemia has been demonstrated by Koessler and associates (2). In experiments on rats subject to diets in which the vitamins were insufficient or lacking, Weitbrecht (18) found that fat in the form of olive oil caused a more rapid fall of blood cells and hemoglobin and a shorter course before death supervened, than the standard vitamin free diet alone. Anemia was not found in all the animals fed on a fat and vitamin free diet. The author therefore concluded that for the production of anemia constitutional factors are necessary. The anemia which occurred in the animals fed with fat as well as in the older adipose animals fed on a vitamin free diet ran a more severe course and went into an aplastic form. As an explanation for this Weitbrecht considered either an injurious effect of the fat in itself, or a similar effect from the fat in a vitamin free milieu. McCarrison (19) also found that a degree of avitaminosis producing a certain train of symptoms including anemia in pigeons and monkeys in the presence of excess starch, will do so twice as rapidly if there is also an excess of fat, i.e., an excessive intake of energy bearing constituents will produce symptoms with an incomplete avitaminosis as rapidly as a complete avitaminosis with energy bearing constituents not so excessive. He concludes that the greater the intake of fat and starches the greater must be the intake of vitamin B.

From the experiments by Weitbrecht and McCarrison with vitamin

deficiency the conclusion may perhaps be drawn that fat as such is injurious because it is an energy bearing substance in a vitamin deficient milieu, and that growth, maintenance and consequently the activity of the blood forming organs is impaired through the lack of the essential vitamins. That butter fat as such, all the other constituents of the diet being satisfactory, does not injure or inactivate blood formation or increase blood destruction in rats, the experimental animal of preference in nutritional studies, has been definitely shown in this study.

To summarize, therefore, young rats will grow to adult size, adult rats will maintain and add to their weight on a diet containing 86.5 per cent of the total calories as butter fat, fed over a period of eight months, without the development of an anemia and without any apparent injury to the blood-forming organs.

CONCLUSIONS

The effect of a diet with 86.5 per cent of the caloric intake in the form of butter fat was studied on growing and adult rats, with reference to growth, maintenance, blood formation and blood destruction, over a period of eight months.

- 1 Young rats grew to adult size and adult rats maintained and added to their weight.

- 2 There was no evidence of injury to the blood-forming organs in either group. Slightly lower, but well within normal, hemoglobin values in the growing rats may, perhaps, be explained as the result of somewhat deficient intake of salts due to the high caloric diet.

- 3 Dry, thin fur was observed in the adult group and in one of the growing rats. A scab-like eruption was present in one of the adult rats.

- 4 The caloric intake per 100 grams of live weight decreased with the duration of the experiment in both groups.

- 5 The necropsy findings were normal except for increase of the abdominal fat and fatty infiltration of the liver in 6 out of 7 cases studied.

- 6 The bone marrow showed slight increase in fat cells with normal blood-forming constituents.

I am indebted to the late Dr. Francis W. Peabody, who suggested the experiment and it gives me great pleasure to acknowledge his valuable advice.

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A NEW PROCEDURE FOR DETERMINING BLOOD SEDIMENTATION RATES

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A new method has been developed for clinical determinations of the sedimentation rates of red blood cells. It differs from the methods generally in use in that (1) Heparin¹ is employed as the anticoagulant (2) Special tubes² are employed for the actual sedimentation, which are 12.0 cm. in height over all and have an inside diameter of approximately 3.80 mm. The lower ends of the tubes are sealed flat, and graduations are placed every two millimeters from the bottom to a height of 100 mm. The capacity up to the zero mark (100 mm.) varies from 1.11 to 1.18 cc.—the capacity being etched upon the glass by the manufacturer at the time of the original calibration (3) Results are expressed in terms of the percentage of total possible settling which occurs during the observation period—one hour.

DETAILS OF METHOD

Collection tubes (15 cc. graduated centrifuge tubes are convenient) are prepared by introducing 0.1 cc. of a solution of heparin containing 1.5 mgm. of the anticoagulant (75.0 mgm. heparin in 50 cc. distilled water), and evaporating off the water in an electric oven or otherwise. This leaves a thin film of finely dispersed heparin in the bottom of each tube, sufficient under ordinary circumstances to prevent coagulation in 50 cc. of blood for twenty-four hours. The tubes are stoppered to prevent contamination.

¹ Heparin may be obtained from Hynson, Westcott and Dunning, Baltimore, Maryland.

² These tubes have been manufactured for us by Macalaster Bicknell Company, 40 Wendell Street, Cambridge, Mass.

When a specimen of blood is desired it is drawn directly into the centrifuge tube by means of the arrangement indicated in figure 1, or is taken first into a syringe and then introduced into the tube containing the heparin. The latter procedure permits blood to be

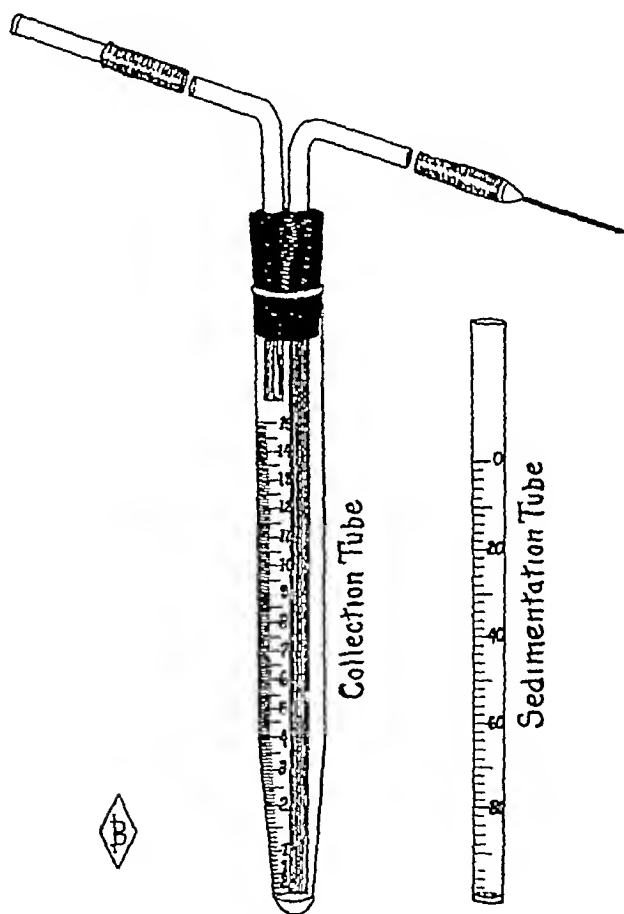


FIG 1 BLOOD COLLECTION TUBE AND NEW BLOOD SEDIMENTATION TUBE

taken at the same time for blood chemistry or for other purposes where its mixture with heparin might be a distinct disadvantage. In any case thorough mixture with the heparin must be secured. Shaking may be resorted to, since aeration of the blood has little effect upon the rate of sedimentation. When very accurate deter-

minations are essential, collection under oil has been adopted, but for clinical purposes is not necessary

With a pipet drawn out to a long, fine point so that it may pass easily to the bottom of the sedimentation tubes and graduated roughly at 1.25 cc, a part of the specimen is now transferred to a sedimentation tube so that the meniscus is at the zero mark. The tube is placed in a vertical position and allowed to stand undisturbed for one hour, when a reading of the height of the clear plasma column is noted on the millimeter scale. The tube is now centrifuged for 20 minutes at a speed of approximately 2500 r p m, and the height of the plasma column read again. This latter reading gives directly the percentage of plasma in the specimen, or the total possible settling in millimeters. By dividing the millimeters of clear plasma obtained after one hour settling by the millimeters of clear plasma after centrifuging, and multiplying by 100 one obtains directly the percentage of total possible settling which has occurred in one hour—the final value.

If the top of the original blood column = 0 the top of the cell column after the end of 1 hour = 20 mm and the top of the cell column after centrifuging = 60 mm, $\frac{20}{60} \times 100 = 33.3$ per cent of total possible settling in 1 hour

RESULTS

The sedimentation rates of certain presumably healthy young adults (22 men and 45 women) have been determined by this method with the results given in table 1.

It should be noted that the sedimentation rate is higher in women (average—30.9 per cent) than in men (average—11.4 per cent), a fact which has been noted by all previous investigators. It is also apparent that the plasma volume percentage is higher in women (average—56.5 per cent) than in men (average—50.8 per cent), an observation which partially explains the more rapid settling in the former. We have been unable to determine any definite relation between the sedimentation rate in women and the period in the menstrual cycle at which the specimen was obtained. Of the six women who had sedimentation rates above 50 per cent, one had just begun to menstruate and one was about due, while the others reported

TABLE 1
Normal values

Case number	Plasma after 1 hour	Plasma after centrifuging	Percentage of total possible settling in 1 hour
Healthy young men			
	<i>mm</i>	<i>mm</i>	<i>per cent</i>
1	6	49	12
2	6	52	12
3	2	46	4
4	9	52	17
5	6	48	12
6	5	50	10
7	4	52	8
8	6	51	12
9	6	49	12
10	6	50	12
11	2	52	4
12	5	53	9
13	9	52	17
14	5	50	10
15	5	51	10
16	10	54	19
17	6	51	12
18	1	48	2
19	11	53	21
20	9	50	18
21	3	49	6
22	6	53	11
Healthy young women			
1	14	54	26
2	23	59	39
3	22	58	38
4	32	62	52
5	22	57	39
6	10	53	19
7	20	61	33
8	23	58	40
9	15	56	27
10	23	58	40
11	8	57	14
12	32	56	57
13	23	57	49
14	18	55	33
15	7	58	12

TABLE 1—*Continued*

Case number	Plasma after 1 hour	Plasma after centrifuging	Percentage of total possible settling in 1 hour
Healthy young women— <i>Continued</i>			
	mm.	mm	per cent
16	18	57	32
17	17	54	31
18	20	58	34
19	20	54	37
20	32	55	58
21	26	55	47
22	18	56	32
23	12	57	21
24	34	59	58
25	29	56	52
26	15	55	27
27	8	52	15
28	19	56	34
29	5	54	9
30	12	54	22
31	11	53	21
32	25	59	42
33	32	57	56
34	20	57	35
35	5	57	9
36	7	56	13
37	10	54	16
38	8	56	14
39	8	58	14
40	21	58	36
41	14	55	25
42	14	62	23
43	9	57	16
44	15	58	26
45	10	56	18

the onset of the previous period 13 days, 21 days, 6 days, and 25 days earlier, respectively. Repeated determinations on the blood from normal individuals has shown that the sedimentation rate varies only very slightly from week to week.

By reason of the range of values obtained upon our series of healthy young women, supported by our clinical experience with the test, we have placed the upper limit for normal in women at 65 per cent,

and look upon higher values as indicating the presence of some physiological or pathological condition associated with abnormally high sedimentation rates. Our experience with the blood of healthy men leads us to place the upper limit of normal at approximately 25 per cent.

DISCUSSION

Heparin is used as the anticoagulant because we have shown that it does not affect the settling rate or the cell volume in any concentration which might reasonably be used to prevent coagulation. The inorganic anticoagulants usually employed (sodium citrate and potassium oxalate) retard the sinking of the cells in proportion to their concentration, and unless used in isotonic solutions interfere with the size of the blood cells and so disturb the plasma volume readings. Moreover, when they are used in solution and a certain amount of blood is specified to be drawn into a given amount of anticoagulant solutions (Linzenmeier (1) and Westergren (2) methods, and their modifications) in a graduated syringe, accurate mensuration becomes difficult, if not practically impossible. As Bonniger and Herrmann (3) have emphasized, even absolute accuracy would not be of much value, since the fluid introduced actually dilutes the plasma, the amount of which in a given specimen of blood is unknown when the dilution is made, unless a preliminary hematocrit is done. If a blood contains 50 per cent of cells by volume and is diluted 4 parts to 1 part of anticoagulant solution, the plasma is diluted 2:1, whereas if the blood contains only 25 per cent of cells by volume and the same dilution is effected, the plasma becomes diluted 3:1. Certainly the use of an anticoagulant solution introduces factors which can not be controlled but which have a definite effect. When even accuracy of dilution is so obviously impossible, it becomes apparent that the whole determination, when carried out by the more commonly used methods, is little more than an approximation. By the use of dried heparin, dilution is entirely avoided, and its attendant difficulties and errors are eliminated. Rubin and Smith (4) have used dry hirudin as an anticoagulant with the assumption that it avoids the errors inherent in the inorganic anticoagulants. Bonniger (5), on the other hand, reports that hirudin

blood generally settles more slowly than untreated blood, and that the sedimentation rates in hirudinized bloods and in oxalated bloods for the most part agree. We have found in a few experiments that bloods taken over hirudin settle somewhat more slowly than those taken over heparin, even though the slowing is not as marked as when solid oxalate is employed. Heparin has one disadvantage—it costs about one cent per milligram.

The total length of the column of blood is probably the most important of the physical factors involved and yet relatively little attention has been paid to securing uniformity in this respect. Sedimentation tubes of the size we use provide for a column of blood of the same height in all tests, and are, moreover, of such a caliber that the accelerating effect of capillary action is small. The total amount of blood which we use is moderate and duplicate determinations can easily be made from an original sample of 3 to 5 cc. We have found that duplicate readings agree within such a small percentage that for clinical purposes a single reading only is made.

One hour has been selected as the most useful period for a single reading, since at that time sedimentation in normal bloods is damped neither by preliminary agglutination nor by packing. As a close approximation, it may be said that when the plasma volume is 60 per cent or less a retardation of the settling rate becomes apparent by the time the top of the cell column has reached the 40 mm mark. Therefore, in rapidly settling bloods packing has usually become effective within the one-hour period, but is of no importance if one takes the view that the test is of more value as a negative finding, i.e., a slow sedimentation rate is more accurately evaluated than is a rapid sinking. The advantage of making readings after a given time interval rather than determining by frequent readings the time necessary for the blood to settle a certain number of millimeters (Linzenmeier (1) method) is obvious. Most recent workers have adopted this point of view, although the Linzenmeier method, which is perhaps used more than any other in this country, is based upon the other principle.

By centrifuging the blood in the sedimentation tubes at the end of the one hour period of settling, we determine directly and with sufficient accuracy the total plasma volume, and are thus in a posi-

tion to correct our results partially for variations in cell volume, which have a pronounced effect upon the rate of sedimentation. A reduced cell volume increases the rate of settling even though other factors which may influence this rate are not disturbed. By diluting centrifuged cells with their own plasma to different cell volumes and then determining the rate of sedimentation, this fact can be demonstrated easily. This means practically that every patient with an anemia of any consequence will have a rapid sedimentation rate, even though no other cause leading to rapid settling may be operative. Obviously this confuses the interpretation of results and is particularly annoying if one emphasizes especially the value of a normal settling rate. By introducing in our calculation the plasma volume percentage as determined by centrifuging the blood (blood volume minus cell volume) as representing the total possible settling, and computing the sedimentation rate as the percentage of total possible settling occurring during the one-hour observation period, we are avoiding some of this difficulty. An alternative procedure, the compilation of a chart showing the settling of different concentrations of normal cells in their own plasma, would undoubtedly be more accurate, but the method adopted is somewhat simpler and has been shown by a year of clinical test to be quite satisfactory. Our experience does not agree with that of Rubin and Smith (1 c), that, "the cell volume obtained by hematocrit bears a fixed ratio to that obtained by the spontaneous settling of the cells in twenty-four hours

" Among 10 normal men in our series, the settling in 24 hours represented from 62 to 77 per cent of the total possible settling (hematocrit), whereas among 35 women it ranged from 65 to 95 per cent. In general, it may be said that the amount of spontaneous settling bears a closer relationship to the sedimentation rate than to the cell volume,—the more rapidly the cells settle, the more nearly complete is the spontaneous settling in 24 hours. In pathological bloods, the variations are even greater than in the normals quoted. Moreover, we prefer to have the final reading available as soon as possible, and for that reason alone would choose centrifugalization.

The complete data, upon which some of the statements in this paper are based, will be presented in a later communication, as will also the results of the clinical application of the test in a large series of obstetrical and gynecological patients.

SUMMARY

A new method is advanced for the determination of sedimentation rates as a clinical procedure. The technic described obviates some difficulties inherent in the methods now in common use. Heparin is employed as the anticoagulant, special tubes are used giving a column of blood 100 mm high, and results are expressed as the percentage of total possible settling (plasma volume percentage determined by centrifuging), which occurs during the one-hour period of observation.

The results obtained on the bloods of 22 normal men and of 45 normal women are reported.

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STUDIES IN BLOOD COMPOSITION OF ANIMALS UNDER PATHOLOGICAL CONDITIONS

I BRONCHO PNEUMONIA IN COWS

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INTRODUCTION

According to Myers (4) and others the development of severe pneumococcus pneumonia in human subjects often entails a more or less pronounced impairment of renal function, apparently secondary to the pneumonia. At the time of the crisis some increase in the non-protein nitrogen of the blood was found, due chiefly to a rise in the undetermined fraction. When the urea nitrogen exceeds 20 mgm there is generally some creatinine retention. Recently McIntosh and Reiman (5) found that serious impairment of kidney function during lobar pneumonia was not encountered. Berger and Petschacher (1) and others showed also that in man there is in pneumonia a marked rise in the globulin fraction of the blood serum. In broncho-pneumonia most patients show a decrease in the blood chlorides before the crisis.

It seemed of value to find out what changes take place in the chemical composition of the blood in bovine pneumonia due to bipolar organisms (*B. bovissepticus*).

MATERIAL AND PROCEDURE

Eight cows, isolated from a herd on account of more or less high temperature and clinical symptoms of pneumonia of various degrees of severity, were bled from the jugular vein (40 cc) and the blood plasma (oxalated) analyzed for glucose (Folin and Wu's method), chlorine (Whitchorn's method), non protein nitrogen (Folin and Wu's method), uric acid (Benedict's method), creatinine (Folin and

TABLE 1

Number	Date of introduction into herd	Date first symptoms were noted	Temperature	Symptoms	Termination
	1927	1927	°C		
5	October 5	October 10	Normal	Atypical case, emaciation, inappetence, diminution in milk, slight lung involvement	Quarantine, 31 days
6	September 9	October 28	40 for 3 days, then relapse, after 7 days, 40-40.1 for 2 days	Typical case, dyspnea, bronchial breathing, inappetence, diminution in milk	Recovered, sick 29 days
7	October 7	October 25	41	Typical case, dyspnea, bronchial breathing, inappetence, diarrhea, diminution in milk	Recovered, sick 36 days
8	Native	November 8	40.3	Atypical, continual coughing, diminution in milk, emaciation, crepitant râles, constipation	November 25, slaughtered
9	October 5	November 3	39.3	Typical case, dyspnea, emaciation, constipation, lessened milk secretions, bronchial breathing	Recovered, sick 21 days
10	July 8	October 20	40.4	Typical case, dyspnea, crepitant râles, mucous membranes pale, rapid pulse, diminution in milk	October 27, sold to butcher Carcass condemned Autopsy lobular pneumonia, fatty degeneration of liver
11	October 5	November 15	40.1-40.5 for 3 days 39	Atypical case, mild form of pneumonia	Recovered, sick 9 days
12	October 15	November 15		Atypical case, mild form of pneumonia	Recovered, sick 9 days

Wu's method), cholesterol (Bloor's method), and albumin, globulin and fibrin (Wu and Ling's method (8)). Control analyses were carried out on the blood plasma of four normal cows

TABLE 2
Blood constituents in normal and pneumonia cows
(Figures per 100 cc. of blood plasma)

Date	Number	Diagnosis	Glucose mgm.	Chlorine mgm.	Non-protein nitrogen mgm.	Uric acid mgm.	Creatinine mgm.	Cholesterol mgm.	Albumin gm.	Globulin gm.	Fibrin gm.
October 25	1	Normal	66.6	386	23.12		1.43	133.2	3.49		
November 7	2		62.4	368	20.69		1.36	144.3	3.49	2.36	0.274
November 7	3		71.6	388	22.22		1.30	88.2	3.34	2.82	0.226
November 7	4		70.8	386	17.65		1.25	100.9	3.72	3.96	0.251
October 31	5	Pneumonia	71.2	338	52.14		2.34	73.2	2.33	4.64	0.411
November 6	5		62.5	356	26.50		1.36	82.5	2.26	5.14	0.411
November 30	5		69.0	334	30.04	1.87	1.90	83.2	2.56	6.56	0.377
October 31	6		64.3	358	20.70			89.0	2.84	3.70	0.452
November 10	6		57.1	346	28.90		1.20	88.2	3.07	3.46	0.502
November 17	6		55.3	326	33.40		1.16	100.2	3.34	3.18	0.411
November 30	6		55.3	364	20.72	1.82	1.25	125.0	3.72	4.30	0.361
October 31	7		59.0	334	19.20		1.25	78.2	2.40	3.82	0.502
November 10	7		57.1	346	25.00		1.02	75.0	2.40	3.22	0.411
November 17	7		54.0	388	30.00		1.16	94.6	3.27	3.74	0.452
November 7	8		57.5	364	21.43		1.20	150.0	2.40	3.22	0.452
November 10	8		62.5	344	24.00		0.94	150.0	2.40	4.16	0.502
November 17	8		64.3	359	26.63		1.14	150.0	3.18	4.18	0.479
October 17	9	Pneumonia	58.4	353	28.56		1.20	136.0	3.36	4.52	0.476
October 30	9		54.1	382	17.15	1.58	1.20	107.0	3.72	4.04	0.452
October 25	10		83.4	388	24.00		1.36		2.33		
November 17	11		57.1	365	30.25		1.25	88.8	3.65	3.26	0.502
November 17	12		58.4	350	20.06		1.07	115.3	3.49	3.42	0.565

The clinical data concerning the eight pneumonia cows are summarized in table 1

A bacteriological examination of the blood and urine of cow 5 was made by Dr F S Jones of this department. The blood culture was negative. He found in the urine albumin, leucocytes, epithelial cells and bacilli in large numbers. Cow 8 was slaughtered and autopsied by Dr Jones and the junior author. The autopsy showed pleuritis and diffuse chronic pneumonia. The presence of *Bacillus bovisephus* was established by direct culture of bits of lung tissue.

RESULTS

The results are summarized in table 2.

As can be seen from the table, cases 5, 6, 7, 8, and 9 show deviation from normal in the amount of chlorine, non-protein nitrogen, and protein fractions. The globulin is high. Cow 5 shows on October 31 a high non-protein nitrogen and creatinine. In cow 6 the cholesterol went up. In cows 11 and 12 (mild cases) the globulin was normal. In pneumonia the fibrin also is usually increased.

DISCUSSION

Chlorine Pneumonia in the cow is evidently associated with a drop in the plasma chlorine, as it is in human beings. The rise in the plasma chlorine seems to be associated with the process of recovery. In cow 8 there was no complete recovery and the chlorine remained below normal. Cow 9 recovered completely and the chlorine reached a normal level also. Cow 5 did not recover up to November 30 and her plasma chlorine was low. Cow 6 recovered. Her chlorine content was, on November 30, normal also. The data reported by Winterstein (7) for normal cattle serum are 369.8 mgm per cent.

Non-protein nitrogen This blood constituent is higher when the process in the lungs is not completely healed, and reaches a normal level during recovery. The high non-protein nitrogen in cow 5 (on October 31) is a symptom of a secondary involvement of the kidneys, as confirmed by the analysis of the urine. The high creatinine content of the blood plasma of the same cow on October 31 is an additional diagnostic sign. Winterstein (7) reports for cattle 14 mgm per cent as normal figures for non-protein nitrogen of blood serum and 1.62 for creatinine. Scheunert and Pelchrzim's (6) figures are

23.8 to 39.4 mgm per cent for non-protein nitrogen and 1.5 to 1.8 mgm per cent for creatinine in normal cattle

Plasma proteins The high globulin is evident in the presented cases 5, 6, 7, 8, and 9 of pneumonia cows. It is not possible to say definitely what caused this rise in the early stage of the disease—the process in the lungs or a certain stage of starvation due to diminished appetite. Keese (3) showed that in horses starvation of 16 to 45 hours causes a considerable rise in the globulin fraction of the blood serum, the latter being sometimes 80 per cent of the total protein content of the serum, while in normal horse serum the globulin fraction is only 50 per cent of the total serum proteins. As our pneumonia cows showed a normal appetite during the time when the temperature went down, it is evident that the high blood serum globulin, found at this time, was due to pneumonia.

A calculation of the relative proportions of globulin nitrogen and albumin nitrogen to the total nitrogen, performed by Howe (2), gives for virgin heifers 49 per cent of the total serum protein as globulin and 51 per cent as albumin, for the pregnant heifers Howe's figures are 51 per cent of total globulin nitrogen and 49 per cent of albumin nitrogen. Our figures for serum globulin are seen to rise much above our normal figures and also those of Howe.

SUMMARY AND CONCLUSIONS

1. Pneumonia in the cow causes a drop in the blood plasma chlorine and a rise in the globulin and fibrin fractions. High non-protein nitrogen and creatinine is a symptom of secondary kidney involvement.

2. In pneumonia cows chemical analysis of blood furnishes valuable data for diagnostic and prognostic purposes.

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STUDIES OF THE CHEMICAL MECHANISM OF HYDROCHLORIC ACID SECRETION

I ELECTROLYTE VARIATIONS IN HUMAN GASTRIC JUICE

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INTRODUCTION

The literature on the chemistry of gastric secretion contains extensive data concerning hydrochloric acid variations and numerous studies of the changes in concentration of chloride but there are very few observations on the other electrolytes. In the present investigation fluctuations in the base, phosphate and chloride were determined in human gastric juice. It was expected that the data thus obtained would give some indication of the mechanism by which a strongly acid secretion is produced from slightly alkaline blood and possibly some insight into the pathology of gastric secretion. While this work was in progress the account of the beautiful and significant experiments of Gamble and McIver (1) appeared showing the relative changes of base and chloride in the secretion of the Pavlov pouches of dogs.

METHODS

In any study of the chemistry of gastric contents special care must be taken that one is dealing with actual secretion. It is remarkable that only in the past few years has much rational consideration been given to the influence which factors inherent in methods may have on the results obtained from gastric analysis. Gorham (2) appears to be chiefly responsible for calling attention to these factors which are rather obvious but had never been properly emphasized. By far the most important factor is the influence of dilution which may be affected by the test meal itself. Gorham used 400 cc. of water to stimulate the secretion. In the water he placed phenolsulphonephthalein. Assuming that no significant amounts of either water or phenolsulphonephthalein were absorbed by the stomach, he calculated the water in the secretion by means of the percentage of

phenolsulphonephthalein which remained. In the following studies this procedure has been used as carefully as possible and the results of analysis have been corrected accordingly.

Subjects were studied in the morning while fasting. They were instructed to drink no water and to swallow no saliva until the examination had been completed. The studies were usually made an hour or more after the usual breakfast time. At this late hour it was surprising how frequently considerable acid was found in the fasting contents. It seemed possible that we might be dealing with a periodic secretion occurring at the usual time for breakfast. Though the procedure was most often carried out in the laboratories adjoining the wards, patients had seen others eating their breakfasts, and it is possible that the secretion was the result of psychic stimulation. However this may be, numerous acid specimens were obtained without corresponding specimens free from acid and suitable for comparison. After the stomach was emptied as completely as possible the subject was given 400 cc of water containing 1 cc of phenolsulphonephthalein solution usually employed for kidney function tests, about 10 cc of the mixture being withheld to use as a standard. At a given interval the stomach was again completely emptied and the material mixed thoroughly. In a few instances small specimens were obtained at given intervals by aspirating, mixing and returning the secretion several times before a fraction of the contents was preserved for analysis.

The acid and phenolsulphonephthalein determinations were made as soon as possible. The determination of phenolsulphonephthalein was not always satisfactory. Alkalization was usually accompanied by a precipitate of protein which was removed by centrifuging. Occasionally there resulted a slight cloudiness which made comparison with the standard difficult. The possible error was estimated by adding known amounts of phenolsulphonephthalein to gastric juice and following the same procedure. Although errors as high as 15 per cent were sometimes obtained the fact does not seem to detract from the general conclusions to be drawn. Excess strong acid was determined by titrating with Toepfer's reagent to pH 3.7 to 4.0. This will be referred to without further discussion as free hydrochloric acid. By total acid is meant the amount of alkali which was required to produce the first faint color to phenolphthalein. Chloride was determined by the Volhard-Harvey method. Values for phosphate were obtained by the method of Benedict and Theis (3) after removing protein by trichloroacetic acid. In some specimens it was impossible to determine phosphate because of the cloudiness which developed.

Total base was determined by a modification of Fisk's urine method (4). Considerable difficulty was experienced in obtaining accurate results in the presence of phosphates by various adaptations to blood analysis which had been suggested. By modifying the procedure by which sulphate was precipitated with benzidine and by titrating directly, total base could be determined with an accuracy of 1 per cent in inorganic solutions containing 150 mM of base and 10 mM of phosphate. The base in the form of sulfate and phosphate salts was

obtained in a manner essentially the same as that described by Stadie and Ross (5). The residue was dissolved in 10 cc. of water and any slight residue of sulphuric acid was titrated with 0.02 N NaOH. After adding 1 cc. N hydrochloric acid to the solution it was placed on the steam bath for 30 minutes to convert meta phosphate to orthophosphate. A dilute benzidine solution was then added very slowly, one drop at a time with vigorous stirring to prevent adsorption of benzidine phosphate by the precipitate. The 15 per cent stock solution of benzidine hydrochloric acid was diluted one to four and 8 cc. were used in each determination. After about 10 minutes the precipitate was filtered through a 5.5 cm. ash-free filter and the beaker and filter washed with 95 per cent acetone, first with three 1 cc. portions and then with three 3 cc. portions. The filter was then returned to the same beaker, and 10 cc. of water and a drop of 0.08 per cent phenol red added. The contents were heated to boiling and while hot were titrated with 0.02 N NaOH to the first pink color which persisted with further boiling. A considerable error was noted which might be caused by carbonate in the 0.02 N NaOH solution. This solution should be prepared as free as possible from carbonate. During each titration, before the endpoint is reached and while the mixture is still distinctly acid it should be boiled and vigorously stirred for about thirty seconds or more. The base combined with phosphate in determinations upon accurately prepared inorganic solutions was constantly in the proportion of one mM. of base for each mM. of phosphate. To the benzidine titration in the case of unknown solutions, an equivalent correction therefore was added. In this series when phosphate was not determined an arbitrary value of 6 mgm. per 100 cc. was taken in making this correction.

EXPERIMENTAL

Numerous studies of the changes in concentration of chloride in gastric juice have indicated that the curve of chloride secretion is similar to and only slightly higher than the curve of hydrochloric acid secretion. Curiously many of these reports have not included the chloride determinations on the fasting contents. When this has been included the concentration has been similar to that found an hour or so after the test meal. It seems quite probable that the lower concentrations which were found early in the curve were due to dilution by the test meal. Gorham, Stroud and Huffman (6) have made similar studies but corrected their data for dilution and find that the chloride concentration remains about the same throughout. The extent to which dilution may obscure the true electrolyte concentration in the secretion is illustrated in the studies recorded in table 1 where the data both before and after correction are given.

In the tables the concentration for all electrolytes except phosphate is expressed as the equivalent of 0.1 N acid or base per 100 cc of secretion. The notations in the columns headed "time" indicate first whether the secretion was collected from the fasting stomach or after the test meal and secondly the interval between the test meal and the collection.

Some examples of characteristic changes in the electrolytes of gastric juice associated with the secretion of hydrochloric acid are

TABLE 1

Changes in gastric secretion following test-meal showing especially the effects of dilution
(Data are expressed as equivalent cc of 0.1 N acid or base per 100 cc)

Case number	Time	Analysis of gastric secretion as obtained				Corrected for dilution indicated by the phenolsulphonephthalein		
		Base	Chloride	Free HCl	Phenol sulphone phthalein	Base	Chloride	Free HCl
		cc	cc	cc	per cent	cc	cc	cc
12	Fasting	110	99	0		110	99	0
	$\frac{1}{2}$ hour	31.5	51	10	49	62	100	38
31	Fasting	118	120	0		118	120	- 0
	$\frac{3}{4}$ hour	45	54	12	56	102	122	28
22	Fasting	97	85	0		97	85	0
	1 hour	43.5	73	24	25	58	98	32
	1- $\frac{1}{2}$ hour	50	110	53	3	51	114	55
	2 hours	72	102	20	Trace	72	102	20
30	Fasting	104	136	39		104	136	39
	$\frac{3}{4}$ hour	55	135	68	15	65	159	80
28	Fasting	113	107	0		113	107	0
	$\frac{3}{4}$ hour	11.5	24.8	11	80	58	124	5

collected in table 1. The data from the first two cases shows what has been found most frequently, little change in the chloride concentration after a considerable increase in acid. They also show that the increase in acid has been accompanied by a corresponding decrease in base. Less frequently a definite increase in chloride has been noted as is indicated by the next three examples. But even here the decrease in base generally plays the more prominent rôle

This is in agreement with the work of Gamble and McIver (1) on the secretion of Pavlov's pouches in dogs, in which it was found that during hydrochloric acid secretion the chloride level remained relatively constant but the base fell in proportion to the increase in acid. In table 2 are grouped thirteen studies where specimens containing free hydrochloric acid were obtained shortly after satisfactory specimens of fasting gastric contents, i e., fasting specimens which did not

TABLE 2

Examples of the usual changes in gastric secretion associated with hydrochloric acid production

(The data have been corrected for dilution and are expressed as the equivalent cc. of 0.1 N acid or base per 100 cc.)

Case number	Fasting					Interval	After test meal				Phosphate
	Base	Chloride	Free HCl	Total acid	Phosphate		Base	Chloride	Free HCl	Total acid	
	cc.	cc.	cc.	cc.	mgm. per cent	hours	cc	cc	cc	cc	mgm. per cent
1	77	94	0	15	6.0	$\frac{1}{2}$	53	89	28	50	5.0
4	95	97	0	18	5.3	$\frac{1}{2}$	70	95	10	14	4.3
8	116	103	0	14	4.8	1	52	97	52	68	6.8
9	104	94	0	15		$\frac{1}{2}$	71	85	22	38	
12	110	99	0	31		$\frac{1}{2}$	62	101	38	94	
15	101	82	0	4	6.9	1	56	100	32	51	4.8
15	122	102	0	3	8.6	$1\frac{1}{2}$	61	111	27	41	7.4
17	103	96	0	15		1	71	84	10	26	
22	97	85	0	19	5.9	1	58	98	32	60	6.7
22	97	85	0	19	5.9	$1\frac{1}{2}$	51	114	55	69	5.3
33	97	85	0	19	5.9		72	101	20	40	5.6
28	113	107	0	12		$\frac{1}{2}$	58	124	55	75	
31	118	120	0			$\frac{1}{2}$	102	122	22		
Average	104	96	0	15	6.2		64	102	31	52	5.5

contain free acid. The data here, and in the remaining tables, have been corrected for the dilution. The average of this group probably illustrates more exactly the usual changes during hydrochloric acid secretion. We may consider the averages of the two groups as ordinary specimens of gastric chyme the second containing in 100 cc the equivalent of 31 cc of free hydrochloric acid. With this increase in hydrochloric acid the total chloride increased only the equivalent of 6 cc. but there was a decided drop of 40 cc in the base.

It appears that, during hydrochloride acid production by the stomach, chloride continues to be secreted at about the same concentration as in the fasting state. This is somewhat similar to the concentration of chloride in serum. In other words chloride ions and water leave the blood at the same relative rate, maintaining

TABLE 3

Analysis of gastric chyme from cases with achlorhydria

(Data are expressed as equivalent cc of 0.1 N acid or base per 100 cc)

Case number	Time	Base	Chloride	Free HCl	Total acid	Phosphate
		cc	cc	cc	cc	mgm per cent
2	Fasting	92	71	0	4	9.5
2	$\frac{3}{4}$ hour	60	45	0	5	10.9
3	Fasting	111	78	0	11	3.4
3	$\frac{3}{4}$ hour	91	60	0	9	11.6
5	Fasting	83	59	0	9	8.7
5	$\frac{3}{4}$ hour	79	51	0	15	5.9
14	Fasting	66	65	0	0	5.9
14	$\frac{1}{2}$ hour	76	60	0	16	9.9
14	1 hour	65	60	0	20	7.2
14	1 hour	105	99	0	24	9.8
14	1 $\frac{1}{2}$ hours	71	75	0	26	6.2
19	Fasting	85	58	0	0	
19	$\frac{1}{2}$ hour	82	54	0	0	11.8
19	Fasting	72	68	0	12	8.5
19	1 hour	111	81	0	0	10.4
19	1 $\frac{1}{2}$ hours	87	67	0	3	9.7
19	Fasting	73	50	0	11	9.5
19	2 hours	73	48	0	9	8.7
20	Fasting	65	48	0	1	4.1
20	1 hour	92	49	0	2	7.6
20	1 $\frac{1}{2}$ hours	82	46	0	3	10.5
25	Fasting	92	74	0	0	10.2
25	$\frac{3}{4}$ hour	107	75	0	0	
Average		84	50	0	8	8.7

about the same relationship as in the serum, acid is freed by retention of base.

The extent of the variations found in a larger number of specimens of gastric juice are recorded in tables 3, 4, 5 and 6, specimens being grouped according to their acid content. The first and second groups (tables 3 and 4) contained no free hydrochloric acid. Those in the

first group (table 3) were from cases which, as far as could be determined, were examples of true achlorhydria. All were cases of pernicious anemia except two, one (case no 3) was considered a case of sprue, the other (case no 14) an instance of post-diphtheritic neuritis, which later, after marked improvement again showed ability to secrete acid. In table 3, the electrolytes showed a rather striking contrast to the specimens without free hydrochloric acid of table 4

TABLE 4

Analysis of gastric chyme which contained no free hydrochloric acid. From cases which were known to have the power to secrete acid

(Data are expressed as equivalent cc. of 0.1 N acid or base per 100 cc.)

Case number	Time	Base	Chloride	Free HCl	Total acid	Phosphate
		cc	cc	cc	cc	mgm. per cent
17	Fasting	98	106	0	8	4.5
17	$\frac{1}{2}$ hour	128	104	0	23	15.5
17	Fasting	95	94	0	1	5.5
17	1 hour	93	104	0	11	8.2
17	Fasting	85	109	0	25	6.5
17	Fasting	103	96	0		
12	Fasting	110	99	0	30	
13	Fasting	130	117	0	18	4.6
15	Fasting	101	82	0	4	6.9
15	Fasting	122	102	0	3	8.6
15	2 hours	126	100	0	14	8.7
15	Fasting	123	92	0	5	8.1
4	Fasting	95	97	0	18	5.3
8	Fasting	116	103	0	14	4.8
9	Fasting	104	94	0	15	
31	Fasting	118	120	0	21	
22	Fasting	97	85	0	19	5.9
28	Fasting	113	107	0	12	
14	1 $\frac{1}{2}$ hours	93	109	0	14	13.7
Average.		103	101	0	14	7.6

which were obtained from other individuals who were known to have the power to secrete acid. The chloride was quite low and the base was also reduced. The average of this group showed a greater excess of base over the chloride than the next group (26 cc. as compared with 7 cc. equivalent). In the next two groups, tables 5 and 6, the secretion contained various amounts of free hydrochloric acid. In table 5

where the acid never exceeded 30 cc the average concentration of chloride showed little variation from the comparable material without free hydrochloric acid in table 4, illustrating again the decrease in base rather than an increase in chloride when free hydrochloric acid is produced. Specimens showing excessive free hydrochloric

TABLE 5

Analysis of gastric chyme containing moderate amounts of acid

(Data are expressed as equivalent cc of 0.1 N acid or base per 100 cc)

Case number	Time	Base	Chloride	Free HCl	Total acid	Phosphate
		cc	cc	cc	cc	mgm per cent
16	Fasting	84	115	18	30	5.9
17	1½ hours	82	120	2	8	7.0
17	Fasting	82	98	5	17	6.4
17	2 hours	81	101	6	21	6.7
17	1 hours	71	84	10	26	
18	Fasting	99	104	10	15	2.3
21	2 hours	105	121	17	30	
21	Fasting	87	119	17	28	
22	2 hours	72	101	20	40	5.6
23	1 hour	105	128	16	34	17.0
23	Fasting	90	96	8	11	3.7
27	Fasting	116	128	1	18	3.8
1	Fasting	77	94	1	15	6.0
1	¾ hour	53	89	28	50	5.0
4	¾ hour	70	95	10	14	4.3
7	1 hour	89	91	2		
11	Fasting	69	108	15	25	6.0
12	Fasting	78	79	10	30	
14	Fasting	81	90	14		
14	1 hour	75	106	27		
15	1½ hours	61	111	27	41	7.4
9	½ hour	71	85	22		
31	¾ hours	102	122	22		
27	Fasting	80	115	26		5.3
Average		79	104	14	26	5.7

acid are collected in table 6, and exhibit a number of examples of higher chloride concentration. It appears that this group cannot very well be compared with that in table 4, since comparable specimens of gastric juice free from acid were not obtained in most cases. The corresponding fasting secretion generally contained acid and high

chloride In this group are sixteen examples of chloride concentrations higher than that ordinarily found in serum It is not likely that these findings can be explained by errors in phenolsulphone-phthalein determination and thus by excessive correction for dilution Chloride concentrations as high as this have been obtained in pure secretion after histamine stimulation The data indicate that the

TABLE 6

Analysis of gastric chyme containing considerable acid

(Data are expressed as equivalent cc. of 0.1 N acid or base per 100 cc.)

Case number	Time	Base	Chloride	Free HCl	Total acid	Phosphate
		cc.	cc.	cc	cc	mgm. per cent
8	1 hour	52	97	52	68	6.8
10	Fasting	66	97	47	63	
10	1 hour	51	109	68	80	
11	1 hour	57	123	50	60	4.6
11	Fasting	51	118	71	77	
11	Fasting	89	128	32	42	
11	2 hours	91	123	33	77	3.5
16	1½ hours	76	125	43	55	1.2
16	Fasting	70	101	34	38	5.5
16	Fasting	83	133	31	44	4.6
21	½ hour	83	124	41	52	
21	1 hour	100	133	42	51	
21	1½ hours	97	140	39	49	
22	1½ hours	51	114	55	69	5.3
22	1 hour	58	98	32	60	6.7
26	Fasting	90	128	51	64	5.1
28	¾ hour	56	124	55	75	
29	¾ hour	67	128	68	74	2.0
30	¾ hour	65	159	80	88	
30	Fasting	104	136	39	54	
12	½ hour	62	101	38	93	
15	1 hour	56	100	32	51	4.8
27	¾ hour	79	108	31	43	4.6
Average.		73	120	46	62	4.5

stomach can secrete chloride ions at a somewhat higher concentration than in the serum The highest figures which have been obtained approach the molar value of serum total base, or in other words, the level of the serum electrolytes The fact remains that the chloride in gastric secretion does not deviate far from the chloride concentration of the serum

The phosphate fluctuations found in the gastric secretion are of considerable interest. The average variations in tables 3, 4, 5 and 6 are as follows

	<i>mgm of inorganic P per 100 cc</i>
Achlorhydria specimens	8.7
Other specimens without HCl	7.6
With free HCl 1 to 30 cc	5.7
With 31 to 80 cc of free HCl	4.5

It is apparent that the phosphate concentration is almost invariably greater in gastric secretion than in serum. In some in-

TABLE 7

Data showing variations in phosphate grouped according to whether free hydrochloric acid was or was not produced as a result of stimulation

HCl secretion with test meal		No HCl secretion with test meal	
Fasting	After stimulation	Fasting	After stimulation
<i>mgm per 100 cc</i>	<i>mgm per 100 cc</i>	<i>mgm per 100 cc</i>	<i>mgm per 100 cc</i>
6.0	5.0	9.5	10.9
5.3	4.3	3.4	11.6
4.8	6.8	4.5	15.5
6.0	4.6	5.5	8.2
6.9	4.8	8.5	10.4
8.6	7.4	4.1	7.6
5.9	3.7		
5.5	1.2		
4.6	4.1		
5.9	6.7		
Average 6.0	4.9	5.9	10.6

stances it is quite high. From 63 determinations there were nine in which the inorganic phosphorus concentration was greater than 10 mgm per 100 cc. It also seems evident that there is a decrease in phosphate with increase in acid. One would suspect that salts with buffer values like the phosphates might play a prominent part in the mechanism by which hydrochloric acid is secreted by the stomach. There is nothing in this work, however, which would indicate this. In table 7 the data showing variation in phosphate are placed in two groups according to whether free hydrochloric acid was or was not

produced as the result of stimulation. If free hydrochloric acid was produced there was a decrease in phosphate, while if no free hydrochloric acid was produced there was an increase. Studies in this laboratory have shown that saliva contains considerably more phosphate than blood serum, confirming earlier reports in the literature. Any dilution of gastric juice with saliva will therefore result in a higher concentration of phosphate. The subjects of these experiments showed admirable coöperation and, as far as one could detect, swallowed little or no saliva just before or during the period of examination. But this effect cannot be ruled out in any individual case and may possibly account for phosphate fluctuations in some instances. If the secretion of the mucous glands of the stomach is similar to saliva, the possibility of an analogous effect by such secretion is evident. It seems probable that as a result of the secretion of the mucous glands, gastric juice contains more phosphate than blood serum. If hydrochloric acid secretion containing less phosphate is produced in larger amounts than the secretion of the mucous glands, a fall in phosphate will result due to dilution. Or if a stimulus causes an increased activity of the mucous glands with little or no hydrochloric acid production the concentration of phosphate will increase.

The presence of the secretion from mucous glands may also explain certain variations in chloride. Saliva contains relatively small amounts of chloride and any dilution of gastric juice with saliva will result in a lower concentration of chloride. But with the care taken to exclude this factor it must have been relatively unimportant in these studies. It seems reasonable to believe that variations in the relative amounts of mucous gland secretion in gastric chyme may have an important relationship to the low chloride content which has been observed in the secretion from cases with achlorhydria and in those in which alterations in chloride were associated with various degrees of acidity.

CONCLUSIONS

Relatively little change in the concentration of chloride in human gastric fluid attends acid secretion, but, during secretion, the total base falls in proportion to the increase in acid. It appears that

chloride ions and water leave the blood in the same relative concentration as in serum, acid being liberated by a retention of base

The concentration of phosphate in gastric contents is generally much greater than in serum. If stimulation does not result in hydrochloric acid secretion the concentration of phosphate as a rule increases. If much acid is produced, however, the concentration falls. The variation in phosphate may be attributed to fluctuations in the relative amounts of secretion from the mucous glands

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PROTOCOLS

Case 1 A man 35 years old with severe diabetes mellitus complicated by chronic diarrhea. At the time of the gastric analysis he was markedly emaciated and there were several extensive, indolent but freely draining subcutaneous abscesses over his back. Pancreatic ferments were present in the duodenal fluid. Diarrhea was eventually relieved only by hydrochloric acid and atropine per os.

Case 2 A man 59 years old with pernicious anemia complicated by chronic ulcerative colitis and bilateral cataract.

Case 3 A man 35 years old with diarrhea for four years. There was a slight anemia and slight atrophy of the tongue but no neurological symptoms.

Case 4 A man 47 years old complaining of constipation for fifteen years. He had considerable epigastric distress after eating but rarely vomited. No organic disease was demonstrated.

Case 5 A man 45 years old with pernicious anemia. For 6 years he had had frequent attacks of vomiting.

Case 6 A man 74 years old who complained of a dull pain in the right upper

quadrant. He had vomited at infrequent intervals. There was a mass in the right side of the abdomen which X ray showed to be extra-alimentary. This was considered a hypernephroma. His condition was too poor to warrant an exploratory operation.

Case 7 A woman 46 years old complaining chiefly of pain in the epigastrium soon after eating and occasional vomiting. She had had one gastric hemorrhage. The diagnosis of gastric ulcer was not confirmed by X ray.

Case 8 A man 56 years old complaining of abdominal distention and epigastric pains shortly after meals. On several occasions stools contained blood. Diagnosis of gall bladder disease was made.

Case 9 A colored woman 28 years old with pain in the lower abdomen. No diagnosis made other than chronic constipation.

Case 10 A man 20 years old with pain in the upper abdomen about one hour after eating and marked constipation. No organic disease demonstrated.

Case 11 A man 23 years old presenting neurological signs, a residual of epidemic encephalitis. There were no gastrointestinal symptoms.

Case 12 A white woman 44 years old, complaining of a mass in upper abdomen and cramp-like pains after eating. X ray showed the mass was probably liver. Wasserman reaction + + + +. Her condition improved with anti-luetic treatment.

Case 13 A woman 50 years old complaining of headache and pain in the upper abdomen. No organic disease of the gastro-intestinal tract was made out.

Case 14 A boy 18 years old who had diphtheria 2 months before admission to the hospital. Two weeks after the acute symptoms subsided he gradually developed paralysis of the lower extremities and occasionally had regurgitation of food and liquids through the nose. There were no gastro-intestinal symptoms. At the time of the first gastric analysis, symptoms were marked. They had practically cleared at the time of the last examination.

Case 15 A man 41 years old who entered the hospital because of an irregular heart. This was found to be due to auricular extrasystoles. He had had more or less constipation for years but no other gastro-intestinal symptoms.

Case 16 A colored man 49 years old with pain in the abdomen unrelated to meals. There was no nausea or vomiting. No diagnosis was made other than chronic constipation.

Case 17 A man 30 years old complaining of weakness and epigastric distress after eating. No organic disease demonstrated.

Case 18 A woman 22 years old with pain in the epigastrium, usually after meals. The pain radiated to the back and was relieved by belching. No diagnosis other than spastic constipation was made.

Case 19 A woman 48 years old with pernicious anemia complicated with pyonephrosis and hypotension. Duration of symptoms about ten years.

Case 21 A man 51 years old with hypertrophic arthritis of the spine and syphilis. No gastro-intestinal symptoms.

Case 22 A man 51 years old with chronic B coli pyelitis and without any gastrointestinal symptoms

Case 23 A man 26 years old with extensive psoriasis No gastro-intestinal symptoms

Case 24 A man 23 years old with chronic constipation for several years and epigastric distress after meals No organic disease was demonstrated

Case 25 A man 44 years old with typical pernicious anemia

Case 26 A man 44 years old with a multiplicity of complaints including general malaise, pain in the epigastrium and pain in joints There was a moderate degree of chronic constipation No organic disease demonstrated

Case 27 A man 27 years old with central nervous system lues For about two years he had had burning in the epigastrium one hour after meals X-ray of the gastro-intestinal tract was negative

Case 28 A man 54 years old with a diagnosis of syphilis of the cerebro-spinal meninges and bilateral glaucoma There were no gastro-intestinal symptoms except chronic constipation

Case 29 A man 33 years old with a typical history and x-ray findings of duodenal ulcer There had been no vomiting

Case 30 A man 27 years old complaining of chronic constipation, loss of appetite, and weakness for about 8 months No organic disease was demonstrated

Case 31 A man 62 years old with multiple diverticula of distal colon and carcinoma of the colon He had had symptoms for 5 years consisting chiefly of dull epigastric pain Rarely had he had nausea and vomiting There was a history of syphilis and the Wassermann reaction was positive

STUDIES OF THE CHEMICAL MECHANISM OF HYDROCHLORIC ACID SECRETION

II OBSERVATIONS ON THE BLOOD PASSING THROUGH THE STOMACH OF DOGS

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The chemical mechanism by which the stomach secretes hydrochloric acid has been the subject of little experimental investigation. Some doubtful hypotheses have been offered dealing chiefly with the state of equilibrium in a mixture of various electrolytes and the impermeability of tissues for some of the ions (1). Harvey and Beasley (2) suggested the formation of a chloride of an organic base which could set free hydrochloric acid after leaving the gland. Most of the experimental work concerning the production of hydrochloric acid relates to the histology of the gland during secretion, and consists essentially of elaborating the original work of Claude Bernard (3). Information bearing indirectly on the problem is furnished by the studies of Gamble and McIver (4) who investigated the chemical changes which occurred in the secretion of Pavlov pouches in dogs. Similar studies on human gastric juice were reported in the preceding paper of this series. The observations indicated that during the production of acid the chloride concentration in the chyme remains about the same as in serum while the base falls in proportion to the increase in acidity. It appeared that water and chloride ions leave the blood in the same relative concentration as in serum and that hydrochloric acid is liberated by a retention of base.

The following experiments were planned to demonstrate more directly the mechanism by which HCl is secreted. Serum electrolytes of the arterial blood and of the venous blood from the stomach were determined before and during gastric secretion in dogs. In all but one experiment anesthesia was produced by isoamylethyl bar-

bituric acid intra-peritoneally in amounts of about 60 mgm for each kilogram of body weight. Histamine was used subcutaneously to stimulate secretion. In each experiment it was designed to collect venous blood draining from the region of the cardia and lesser curvature where a maximum acid secretion would be expected. Post-mortem examinations in each case showed this had been accomplished. The following protocol of a typical experiment will indicate the procedure adopted in all observations.

Dog number 5 Fasting 24 hours Weight 22 kilograms

12 45 p m 1.4 grams of isoamylethyl-barbituric acid was injected into the peritoneal cavity

1 05 p m The dog was sleeping quietly, only a little mucus, neutral in reaction, was obtained by aspirating through a stomach tube

1 10 p m A median incision was made from the xiphoid to the lower half of the abdomen. The spleen was delivered, care being taken to avoid trauma to the stomach. The splenic vein was then followed backward and upward towards its junction to the portal vein (fig 1). The coronary vein from the cardia of the stomach was identified as it emptied into the splenic vein. Two ligatures were placed around the splenic vein, one distal and one proximal to that portion into which the blood from the cardia was flowing. The needle of a 20 cc syringe was then carefully inserted into the splenic vein between these ligatures and both ligatures drawn taut to prevent any influx of blood from the spleen or from the portal vein. Thus only blood from the cardia was obtained from the isolated segment of the splenic vein.

1 23 p m 30 cc of venous blood from the cardia was secured without exposure to air and transferred to centrifuge tubes under oil.

1 25 p m A specimen of arterial blood was drawn from the previously exposed femoral artery and placed under oil.

1 30 p m By mistake another sample of arterial blood was obtained. Venous blood from leg was intended.

1 31 p m 10 mgm of histamine was given subcutaneously.

1 40 p m 100 cc of water placed in stomach. Reaction of stomach contents was found to be neutral.

1 42 p m 2 mgm histamine was given subcutaneously.

1 50 p m 2 mgm histamine was given subcutaneously.

1 55 p m 1 mgm histamine was given subcutaneously. Stomach contents slightly acid.

2 00 p m 1 mgm histamine was given subcutaneously.

2 05 p m 1 mgm histamine was given subcutaneously.

2 10 p m 1 mgm histamine was given subcutaneously. Reaction of stomach contents strongly acid.

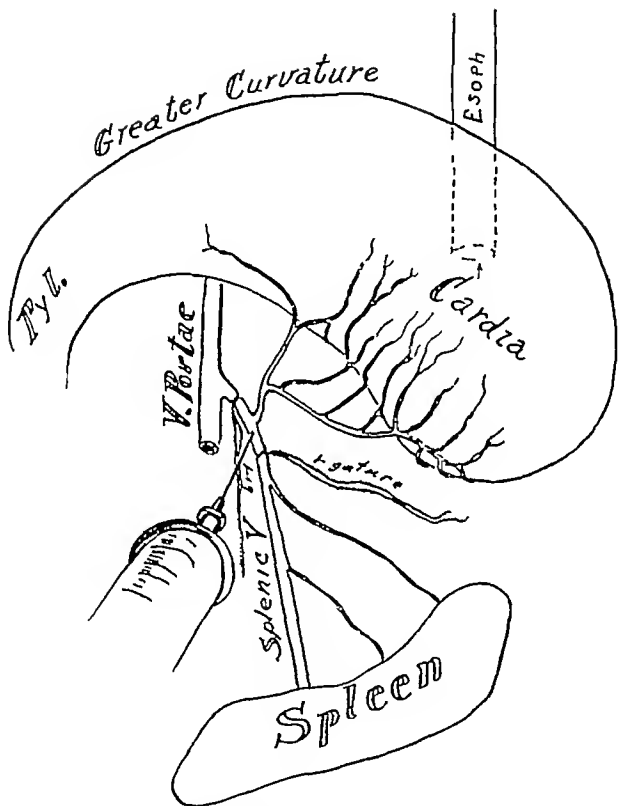


FIG 1 OBSERVATIONS ON THE BLOOD PASSING THROUGH THE STOMACH OF DOG

2 14 p m Sample of venous blood was obtained from the cardia as described above

2 16 p m Sample of arterial blood was obtained from femoral artery

2 18 p m 1 mgm histamine was given subcutaneously

2 24 p m 1 5 mgm histamine was given subcutaneously

2 35 p m 1 5 mgm histamine was given subcutaneously

2 37 p m 30 cc of venous blood was obtained from cardia

2 39 p m 30 cc of blood was obtained from femoral artery

2 44 p m 20 cc of blood was obtained from femoral vein

4 15 p m 30 cc of venous blood was obtained from cardia

4 17 p m 30 cc of blood was obtained from femoral artery

The dog continued to be in good condition The secretion was still acid, but obviously quite small in amount

The animal was killed by opening the chest wall There was no food in the stomach The veins from which the venous blood of the stomach was obtained drained the lesser curvature and the cardia

Blood was collected under oil in pyrex centrifuge tubes and defibrinated by stirring gently with a glass rod The tubes were carefully closed with rubber stoppers and centrifuged The serum was transferred to sampling bulbs without exposure to the air Carbon dioxide was determined by the method of Van Slyke and Stadie (5), chloride by the method of Van Slyke (6) and phosphate by the method of Benedict and Theis (7) Serum protein concentration was calculated from the total nitrogen determined by the Kjeldahl method, after correction for the non-protein nitrogen in the trichloroacetic acid filtrate Some details concerning the procedure used for determining the total base are included in the preceding article (8) For the total base of serum, the protein free trichloroacetic acid filtrate was used in amounts the equivalent to 1 cc of serum for each determination

Data indicating the changes which occurred in the serum electrolytes during HCl secretion are presented in five tables each representing an experiment on a single animal and exhibiting the differences between arterial blood and the venous blood of the stomach Values of the anions are expressed in millimoles of base combining capacity, assuming a ratio of primary to secondary phosphate of one to four and calculating the base combined with protein by a formula devised by Van Slyke, Wu and McLean (9) In the latter calculations and in correcting for the dissolved CO_2 a pH 7.35 was arbitrarily assumed The term total acid is used to indicate the sum of all the determined acids The difference between the determined acids and the total base is taken to represent the organic acid fraction though it contains a small amount of sulfate which was not estimated

If, as is indicated by Gamble's experiments and our studies on human subjects, chloride ions leave the blood in a concentration about the same as in serum, little change in the concentration of chloride in the serum from the secreting stomach would be expected. The tables show that this assumption is correct. As serum passed from the arterial to the venous side of the stomach circulation, the chloride changes were not striking. One hour after stimulating secretion in dog number 3, the chloride concentration in the arterial and venous serum was the same. This was also true in the experi-

TABLE 1

Data from dog number 1, fasting 24 hours amylal anesthesia

Fasting contents neutral. Initial 4 mgm. of histamine subcutaneously followed in 10 minutes by acid secretion. Five subsequent injections of histamine 1 mgm. each, at 10-minute intervals. The second set of blood samples taken one hour after the initial histamine. Although strongly acid only about 40 cc of secretion was obtained in one hour.

	Before secretion		1 hour after stimulation of secretion		
	Arterial serum	Venous serum, stomach	Arterial serum	Venous serum, stomach	Venous serum, leg
	mM	mM	mM	mM	mM
HCO ₃	22.0	22.7	19.1	23.7	24.0
Cl	113.5	109.7	112.1	109.0	110.8
PO ₄	4.0	2.8	4.8	3.9	5.3
Protein	13.3	11.6	12.2	11.1	10.3
Total acid	152.8	146.8	148.2	147.7	150.4
Total base	158.3	157.9	159.0	161.8	159.4
Organic acid	5.5	11.1	10.8	14.1	9.0

ment on dog number 5 after 45 minutes. In nine observations the average fall in chloride was only 1.9 mM, an alteration which is comparable to the changes in chloride noted in the venous blood taken simultaneously from the leg. A decrease in chloride in the serum is therefore not a prominent feature of hydrochloric acid secretion. Chemical changes in the gastric juice indicated that as water and chloride ions were secreted acid was produced by a retention of base. In nine observations on the serum from the secreting stomach there was an average rise of 6.8 mM in the total base of the serum. In

the experiment on dog number 1 where the volume of secretion was rather small the least change was observed. The maximum increase of 11.3 mM was observed in dog number 5 after two and a quarter hours at a time at which the rate of secretion did not appear to be great, but which followed a period of rapid secretion. It is interesting to compare these alterations with similar observations obtained while the stomach was at rest and in the fasting condition. In every instance, with the exception of dog number 8, there was a slight

TABLE 2

Data from dog number 3, fasting 24 hours

In this one experiment the animal was rendered unconscious by a crushing blow on the head under light chloroform anesthesia, anesthesia then discontinued and artificial respiration started. A little mucous in the stomach contained no free acid. Initial histamine 7.5 mgm subcutaneously. Subsequent histamine 6 mgm in divided doses. The first acid appeared in 20 minutes. The first pair of blood specimens collected in 33 minutes, the second in 52 minutes. There appeared to be more rapid secretion in this experiment than any other.

	Before secretion		½ hour after stimulation		1 hour after stimulation	
	Arterial serum	Venous serum, stomach	Arterial serum	Venous serum, stomach	Arterial serum	Venous serum, stomach
	mM	mM	mM	mM	mM	mM
HCO ₃	17.1	19.1	18.6	22.5	19.5	22.0
Cl	114.9	113.0	113.0	110.8	113.9	113.0
PO ₄	2.5	2.8	2.0	2.4	1.8	2.6
Protein	9.1	9.5	8.6	10.0	6.7	7.2
Total acid	143.6	144.4	142.4	145.7	141.7	144.8
Total base	173.7	171.5	171.3	176.8	165.2	171.4
Organic acid	30.1	27.1	28.9	31.1	23.5	26.6

decrease of base in the venous serum from the stomach. The exception observed in dog number 8 could probably be accounted for by the discovery postmortem of undigested meat in the stomach.

Changes such as those observed in the serum would, if not neutralized, yield an exceedingly alkaline blood. Some factors must therefore be operative to compensate for the increase in base and any slight fall in chloride. It is evident that an adjustment is partially effected by a gain in bicarbonate. The magnitude of the increase in bicarbonate during the resting state is often surprisingly small.

During secretion it is more marked. Nevertheless, it is obvious that the bicarbonate supplied fails to accommodate for the entire change. The average increase in base is 6.8 mM, the average decrease in chloride is 1.9 mM, making a total of 8.7 mM which must be neutralized. The average increase in bicarbonate is only 3.4 mM. Organic acids appear to play an equally prominent part. The relative importance of the two varies considerably in the different experiments. In some of the observations an increase in the organic acid fraction was the chief factor. This was especially true with dog number 5 in which after two and a quarter hours the change in

TABLE 3
Data from dog number 5
See sample protocol in text

	Before secretion			½ hour after stimulation		1½ hours after stimulation			2½ hours after stimulation	
	Arterial serum	Arterial serum	Venous serum stomach	Arterial serum	Venous serum stomach	Arterial serum	Venous serum stomach	Venous serum, leg	Arterial serum	Venous serum stomach
	mM	mM	mM	mM	mM	mM	mM	mM	mM	mM
HCO ₃	23.8	23.5	23.3	21.5	24.9	21.3	24.9	23.9	24.0	25.6
Cl	113.0	112.2	111.8	111.8	111.9	110.8	109.0	109.9	110.2	108.1
PO ₄	3.1	3.0	3.0	4.1	4.1	4.1	3.7	4.1	4.2	5.4
Protein	10.7	11.5	11.5	10.0	9.8	10.4	11.4	11.9	10.6	9.1
Total acid	150.6	150.2	149.6	147.4	150.7	149.0	149.0	149.0	149.0	148.2
Total base	175.0	175.0	171.5	189.8	199.8	195.9	193.0	184.3	186.4	197.7
Organic acid	24.4	24.8	21.9	42.4	49.1	39.2	44.0	35.4	37.4	49.5

bicarbonate was relatively unimportant with a striking increase in base. The data in this particular instance indicate a very marked increase in organic acid.

The last three tables include data contrasting satisfactorily the changes observed in the leg with those of the secreting stomach. A simple comparison is made in the experiment on dog number 7 (table 4), where it so happened that during secretion the alterations in bicarbonate and chloride in the venous serum from both the stomach and leg were the same. But the serum from the leg showed only a slight increase in total base and little indication of an increase

in organic acids At the same time there was a marked rise in the total base of serum from blood flowing through the stomach, the excess presumably neutralized by organic acids Essentially the same features were presented in the similar observations recorded in tables 3 and 5

The changes in the concentration of protein during the secretion were not marked Dog number 3 illustrates the type of variation one would expect, an increase with secretion But it was surprising that in other cases the protein was unaltered or even decreased No

TABLE 4

Data from dog number 7, fasting 24 hours, amyial anesthesia

Fasting contents neutral Initial histamine 8 mgm subcutaneously Subsequent histamine 8 mgm during the next hour in divided doses The stomach contents remained neutral for 40 minutes, and then gradually became strongly acid The second sample of blood from the stomach 78 minutes after the initial histamine, the arterial and venous from the leg during the next ten minutes

	Before secretion			1½ hours after stimulation		
	Arterial serum	Venous serum, stomach	Venous serum, leg	Arterial serum	Venous serum, stomach	Venous serum, leg
	mM	mM	mM	mM	mM	mM
HCO ₃	27.6	27.8	28.0	24.1	26.8	26.6
Cl	111.7	110.7	110.6	108.5	106.8	106.8
PO ₄	4.3	4.4	3.9	5.1	4.9	4.9
Protein	8.7	11.0	9.0	10.2	8.4	(10.2)*
Total acid	152.3	153.9	151.5	147.9	146.9	148.5
Total base	195.0	194.4	192.0	185.2	190.7	186.7
Organic acid	42.7	40.5	40.5	37.3	43.8	38.2

* Determination lost, this value assumed

clear explanation of this can be offered In experiments on dog number 5, poor checks were obtained in triplicate determinations, averages were recorded and the results may be erroneous The protein in the secretion would have little influence In these experiments some water was always left in the stomach Significant amounts of fluid may have been absorbed, but even this will not explain the dissociation of the base and the protein variations

In the experiments on human subjects it was shown that the concentration of phosphate in gastric juice is greater than in serum

Therefore one might have anticipated a decrease in the serum phosphate as the blood flowed through the secreting stomach. But there was little change. In fact, the experiments indicate that there may be a slight increase. An increase in phosphate in both the secretion and serum suggests that a liberation of phosphate may be associated with glandular activity. When the experiments were being planned, it seemed possible that the phosphate ions would be intimately related to the process by which a very acid secretion is formed from slightly alkaline blood, but the magnitude of the phosphate changes which

TABLE 5

Data from dog number 8, under amylal anesthesia and supposedly fasting 24 hours, a little mucus from the stomach showed no free acid

Initial histamine 7.5 mgm. subcutaneously. Subsequent histamines 9 mgm., 1 mgm every 5 minutes. Acid first noted 30 minutes after initial histamine. The first blood from the stomach obtained after 55 minutes, the second after 90 minutes. A little undigested meat was found in the stomach postmortem.

	Before secretion			1½ hours after stimulation			
	Arterial serum	Venous serum, stomach	Venous serum, leg	Venous serum, stomach	Arterial serum	Venous serum, leg	Venous serum, stomach
	mM	mM	mM	mM	mM	mM	mM
HCO ₃	23.7	25.8	26.4	25.9	20.6	25.1	25.7
Cl	112.8	111.1	110.3	108.2	111.1	108.2	107.5
PO ₄	3.3	3.1	3.2	3.5	3.2	4.1	3.6
Protein	10.4	11.5	10.7	10.7	10.5	10.6	10.8
Total acid	150.2	151.5	150.6	148.3	145.4	148.0	147.6
Total base	184.0	194.1	186.2	191.4	186.2	186.3	192.8
Organic acid	33.8	42.6	35.6	43.1	40.8	38.3	45.2

are recorded here certainly do not indicate any important relationship.

No mechanism is suggested whereby the weak acids, carbonic and possibly lactic, usual products of cell activity could replace the strong hydrochloric acid. In this connection the suggestion of Harvey and Bensley (2) is interesting. They noted the accumulation of secretion in the lumen of the gland in the rabbit's stomach. Microchemical reactions showed this secretion was not acid until it mixed rather slowly with surrounding salt solution. To them it seemed "probable that the chlorine is secreted by the parietal cells in the

form of a chloride of an organic base and that hydrochloric acid is only set free after the secretion is poured out of the gland into the foveola " Later, Roseman (10) concluded from his experiments that there were two steps in the secretion of gastric acid, chloride accumulation and the splitting off of acid Hanke (11) has presented evidence of the presence in gastric and other tissues of a specific enzyme hydrolyzing organic chloride esters

The results of the present experiments are not in conflict with this concept Secretion thus liberated into the lumen of the glands would be in contact with a relatively large surface Osmotic equilibrium with the blood could quickly be established and a secretion could eventually be obtained which might have chemical characteristics noted in the first paper of this series Under these circumstances a marked change in the total base of serum might occur following the formation of such a hydrochloric acid precursor This is suggested in the experiment on dog number 5 when after two and a quarter hours the secretion of hydrochloric acid had greatly diminished or possibly stopped At this time the serum from the stomach presented the most marked changes observed in any of the experiments Such a process could explain the dissociation of the base and the protein variations in the serum

CONCLUSIONS

- 1 As blood flows through the secreting portion of a dog's stomach the alterations in the concentration of serum electrolytes indicate the chemical mechanism by which a strongly acid secretion is produced

- 2 There is in the serum an increase in the total base with little change in the concentration of chloride

- 3 It appears that chloride ions leave the blood with a proportional amount of water and a strongly acid secretion is produced by a retention of base This relative increase in base is neutralized and equilibrium in the serum maintained by an increase in the bicarbonate and organic salts

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THE EFFECT OF POSTURE UPON THE COMPOSITION AND VOLUME OF THE BLOOD IN MAN¹

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INTRODUCTION

About one year ago, Lindhard (2) reported a few observations on the distribution in the blood stream of vital red injected intravenously. He found that in man, in the sitting position, after a mixing time of 5 minutes, blood from the saphenous vein contained dye in a concentration one-half of that in blood taken from the cubital vein. If, however, the man walked between the time of dye injection and the time of blood collection, the concentration of dye in blood from the two veins was the same. He concluded that, in order to get accurate observations of plasma volume, the subject should walk between the time of dye injection and blood collection. Numerous observations of plasma volume had previously been made by one of us (3) (42) by means of the so-called dye method, in which a similar dye, brilliant vital red, was used. These had already led to the conclusion that, when observations are made exclusively upon blood from an arm vein in a normal man in the horizontal position after a rest period of at least 30 minutes, similar results are always obtained. The contrast between Lindhard's observations and our own made it appear desirable to determine conclusively the effect of posture on plasma volume determinations by the dye method.

Early in our work, we observed that in an individual in the standing still position, the volume of cells per liter of blood, the red count and

¹ A brief account of this work has already been published (1).

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the concentration of dye in arm venous blood were greater than in the recumbent position. It, therefore, appeared highly probable that standing still produced a diminution in the total amount of plasma. The study of the effect of posture on the composition of the blood thus became a second important part of our investigation.

Bohme, in 1911 (4), made several observations, at short intervals, of the refractive index of the serum of ear blood in a man lying down just after walking about. He found that it steadily decreased for about 30 minutes, when a resting level was reached. The change often corresponded to a variation in serum protein of more than 12 per cent. This change was also observed in several individuals when they lay down at the end of a day's work. He also found that the protein concentration was about 5 to 6 per cent greater when the subjects were in the sitting position than when they were lying down.

Cipriani and Moracchini (5) have recently reported determinations of the serum protein on cardiac and nephritic patients of various types by the refractometric method. Blood for the determinations was withdrawn in the morning both before and 4 hours after arising. The patients received no food or water until after the completion of the experiments. In 9 out of 11, an increase in serum protein of 7 to 15 per cent was observed. Two normal persons showed no change under the same conditions. During a control period of 4 hours in bed, no change in the value of serum protein was observed in either the normal or the pathological cases.

We have not found any observations on the effect of standing still on the composition of the blood. It was, however, known to us from the work of Field and Bock (6) that, in this position, marked changes in the circulation may occur.

METHODS

The subjects took no food or liquid after 6 p.m. the day before the experiment. All experiments were preceded by a period of at least 30 minutes in the horizontal position. When taking the standing still position, the subjects were asked to stand with the feet about six inches apart and to remain as *motionless as possible*. In spite of good intentions, they could not avoid slight movements.

Plasma volumes were determined by the dye method of Keith, Rowntree and Geraghty (7) except that brilliant vital red (1.5 per cent solution) was used instead of vital red, and 1.6 per cent sodium oxalate (2 cc. to about 10 cc. of blood)

was used instead of powdered sodium oxalate as an anticoagulant Unless otherwise stated in the tables, the dye was invariably injected into an arm vein (usually the right cubital)

The same sample of blood, collected in calibrated 15 cc centrifuge tubes, and spun at 2500 revolutions per minute for at least 45 minutes, served for the estimation of relative cell and plasma volume and also for total plasma volume Red counts were also made on this sample of blood

For all other determinations, coagulation was prevented by the use of powdered potassium oxalate—about 20 mgm to 10 cc. of blood

Total nitrogen was determined by the Dyer modification (8) of the macro-Kjeldahl method using 2 cc of plasma The non protein nitrogen was determined by the Folin Wu method (9)

Total plasma protein was estimated by subtracting the non protein nitrogen from the total nitrogen and multiplying the difference by 6.25

Plasma water was determined by drying a known amount of plasma to a constant weight in an electric oven at a temperature of 110°C

Specific gravities were done for us by Miss Dorothy Sloane in the surgical research laboratory, using the method of Barbour and Hamilton (10)

Total CO₂ determinations were made for us in Dr Arlie V Bock's laboratory using Van Slyke's method (11)

Chlorides were determined by Van Slyke's method (12)

All of these determinations were made on samples of blood drawn from a cubital vein with the arm held at the side Additional measurements of total plasma volume, red count and cell volume were also frequently made on blood drawn from a foot vein For all determinations other than red count, cell volume and total plasma volume, the blood was collected under oil before injecting the dye.

THE SUBJECTS STUDIED

Cases 2, 7 and 8 were normal individuals

Cases 1, 3, 4 and 5 were cured cases of exophthalmic goitre Case 1 had slight pitting edema of the ankles This was probably cardiac in origin but there were no other cardiac symptoms

Case 6 was a case of myxedema whose metabolism was held at a normal level for 16 months previous to and also during the experimental period

Case 9 had untreated myxedema

EXPERIMENTAL RESULTS

In table 1 the average values and in tables 2 to 4 the detailed figures are given for the nine individuals studied in the horizontal and in the standing still positions

It may be seen that, during the period of standing still, after a rest in the recumbent position, there are the following changes in the blood

- 1 An increase in the number of red cells per cubic millimeter of blood (column I)
- 2 A corresponding increase in the volume of cells per liter of blood (column II)
- 3 An increase in the specific gravity of plasma (column VI)
- 4 An increase in the concentration of plasma protein (column IV)

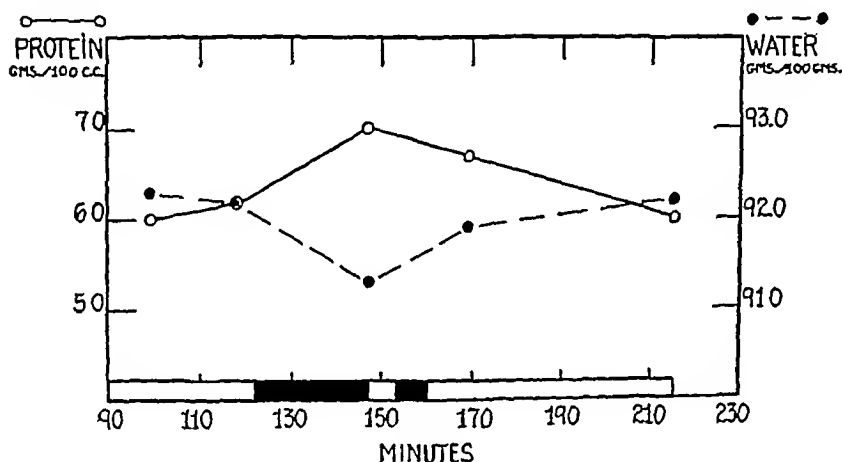


FIG 1 VARIATIONS IN THE CONCENTRATION OF PLASMA PROTEIN AND PLASMA WATER ACCOMPANYING CHANGE FROM THE RECUMBENT TO THE STANDING STILL POSITION FOLLOWED BY THE REVERSE CHANGE (CASE 7, TABLE 4)

White areas denote the recumbent position, and black areas, the standing still position

- 5 A decrease in the concentration of plasma water (column V)
- 6 A decrease in the total amount of plasma in the blood of the whole body (column III)

Upon resuming the recumbent position the changes are reversed (table 4) Data on a typical case are plotted in figure 1

From these observations, it seems safe to draw the conclusion that, while standing still, the blood temporarily loses a much greater volume of fluid than it gains

Average figures showing the effect of posture upon the composition and volume of the blood (all 9 subjects)

Case				I			II			III			IV			V			VI			
Number	Sex	Age	Height cm.	Weight kgm.	Red blood cell count (millions/cumm.)			Cc. of cells per 100 cc. blood			Total plasma volume (cc.)			Protein (grams/100 cc.)			Water (grams/100 grams)			Specific gravity		
					Lyling	Stand- ing	Differ- ence	Lyling	Stand- ing	Differ- ence	Lyling	Stand- ing	Differ- ence	Lyling	Stand- ing	Differ- ence	Lyling	Stand- ing	Differ- ence	Lyling	Stand- ing	Differ- ence
1	♂	55	177	66.4	4.8	5.7	+0.9	44.6	49.6	+5.0	3,055	2,580	-475	7.2	8.3	+1.1	1.91	1.90	-0.01	1.026	1.029	+0.003
2	♂	60	172	57.2	4.4	4.4	+0.0	45.9	48.8	+2.9	2,775	2,445	-330	6.9	8.2	+1.3	1.91	1.90	-0.01	1.026	1.027	+0.001
3	♀	38	152	52.3	4.1	4.6	+0.5	40.1	44.2	+4.1	1,140	1,900	-760	7.0	7.8	+0.8	1.91	1.90	-0.01	1.025	1.029	+0.004
4a†	♀	37	159	60.3	3.9	4.3	+0.4	35.6	38.1	+2.5	2,495	2,195	-300	6.5	7.9	+1.4	1.91	1.90	-0.01	1.028	1.029	+0.001
5	♂	31	171	63.5	4.7	5.1	+0.4	48.0	50.9	+2.9	2,505	2,165	-340	7.0	7.8	+0.8	1.91	1.90	-0.01	1.025	1.029	+0.004
6	♀	43	159	61.3	4.1	4.6	+0.5	28.1	30.2	+2.1	2,755	2,485	-270	6.5	7.9	+1.4	1.91	1.90	-0.01	1.028	1.029	+0.001
7	♀	29	159	45.2							1,810	1,580	-230	6.1	7.0	+0.9	1.92	1.91	-0.01			
8	♂	28	173	80.0							3,200	2,985	-215	7.0	7.5	+0.5	1.91	1.90	-0.01			
4b†	♀	37	159	60.3							2,495	2,305	-190	7.2	7.8	+0.6	1.91	1.90	-0.01			
9	♂	59	171	89.3							2,835	2,525	-310	7.3	8.2	+0.9	1.91	1.90	-0.01			
Average for cases 1 to 6 inclusive					4.3	4.8	+0.5	40.4	43.6	+3.2	2,620	2,295	-325									
Average for cases 3 to 6 inclusive					4.2	4.7	+0.5	38.0	40.9	+2.9	2,475	2,190	-285	6.9	8.1	+1.2	1.91	1.90	-0.01	1.026	1.028	+0.002
Average for cases 3 to 9 inclusive														6.9	7.8	+0.9	1.91	1.90	-0.01			
Average plasma volumes for all cases											2,605	2,315	-290									

* In cases 1 to 6, all plasma volumes, and in cases 4b and 9, those for the horizontal position, were determined by the dye method. In cases 7, 8, 4b and 9, the plasma volume for the standing still position was calculated from the change in protein concentration. In cases 7 and 8, it was arbitrarily assumed to be 40 cc. per kilogram for the recumbent position.

† Case numbers 4a and 4b refer to two distinct sets of experiments on the same subject.

TABLE 2

Detailed figures showing the effect of posture upon the composition and volume of the blood and upon the mixing of the dye (cases 1 and 2)

Case	Date	Time			Millions of red cells per cu mm of venous blood in		Cc of cells per 100 cc of venous blood in		Per cent concen tration of dye* in plasma in the venous blood of		Plasma volume on the basis of the dye concentration in venous blood of the		
		Of assuming position	Of dye injection	Of observation	Right arm	Left arm	Right arm	Left arm	Right arm	Left arm	Right arm	Left arm	
Horizontal													
1 W M	March 28, 1927	10 00 a m	12 30 p m	12 35 p m	4 8		45 9		102 0		2,995		
	April 2, 1927	11 17 a m	1 17½ p m	1 25 p m	4 6		44 4 45 3		99 2 100 9		3,080 3,030		
	May 7, 1927	9 00 a m	1 30 p m	1 35 p m			45 2 45 8 106 0	106 0	102 3		2,880 3,050 2,985		
	May 17, 1927	10 30 a m	1 00 p m	1 06 p m			43 5	43 6 99 2	98 9 3		3,080	3,090	
	June 9, 1927	11 00 a m	2 06 p m.	2 11½ p m.	5 0 4 7 4	8 44 3 44 2 43 6	5 0 45 5 45 8 44 9 103 0	101 9 102 1	97 5 3,090 3,120 3,135		3,105 3,130 3,155		
			Averages***†		4 8		44 6 44 7 44 5 101 1	99 9 99 6 3,025 3,060 3,070	100 2		3,055		
Standing still													
	March 29, 1927	12 09 p m	12 24 p m	12 30 p m	5 1		50 4 50 2 51 5 126 2 124 5	110 0 2,420 2,455 2,780	104 6		2,920		
	March 31, 1927	12 20 p m	12 33 p m	12 45 p m			48 5 49 3	119 6 126 0	2,555 2,425				
				1 05 p m	5 3		50 4 50 8 50 8 120 5 122 5	122 7 2,535 2,495 2,490					
	April 21, 1927	12 55 p m	1 02 p m	1 11 p m			48 3	50 2 119 6	119 3 2,555		2,560		
				1 24 p m	5 4		49 7 49 0 51 2 118 7 118 1	125 3 2,575 2,585 2,435					
				1 44 p m			50 1 50 1 51 7 118 1	122 7 2,585 2,625 2,490					

June 7, 1927	1 09 p.m.	1 17 p.m.	1 23 p.m. 1 31½ p.m. 1 48 p.m.	5 6 5 6	48 9 49 7 50 1 123 0 115 8 101 12 485 2 640 3 020
June 16 1927	2 58 p.m.	3 12½ p.m.	3 19½ p.m. 3 27 p.m. 3 56 p.m.	5 6 5 4	50 1 47 7 51 3 121 0 117 1 119 62 525 2 605 2 555
July 14 1927	2 08½ p.m.	2 12½ p.m.	2 18 p.m. 2 24 p.m. 2 30 p.m.	5 6 5 4	49 4 48 8 51 1 120 0 118 4 77 52 545 2 580 3 940
					48 3 48 8 49 9 110 8 109 0 103 62 760 2 800 2 950
					46 5 48 6 49 8 51 2 119 0 109 5 117 62 570 2 790 2 600
					46 5 47 3 47 5 125 0 124 4 67 02 445 2 455 4 560
					6 1 47 3 48 6 49 0 118 7 114 1 111 82 575 2 675 2 735
					6 3 48 5 46 9 50 4 116 6 113 0 120 22 620 2 705 2 540
					49 0 49 1 50 6 119 1 116 9 120 42 570 2 620 2 540
					49 6
				5 7	118 5
					2,580

Lying followed by standing still**

April 11 1927	10 30 a.m. 1 03 p.m.	12 51 p.m.	12 59 p.m. 1 25 p.m.	4 6 4 7	44 3 44 0 43 1 101 3 100 2 98 33 015 3 045 3 110
					48 3 47 9 48 8 111 4 109 5 116 0 2 740 2 790 2 635

Horizontal

2 P R.	October 16 1926 October 24, 1926 November 14, 1926	8 00 a.m. 8 30 a.m. 8 30 a.m.	9 30 a.m. 10 00 a.m. 9 45 a.m.	9 35 a.m. 10 06 a.m. 9 49 a.m.	4 5 4 2 4 3	48 0 45 8 44 6	101 1 105 0 99 0	2 740 2 640 2,800
				9 52 a.m.	4 5	45 0	95 3	2 910
			Average		4 4	45 9	100 1	2,775

Standing still

October 9, 1926 October 23 1926 November 19 1926†	10 30 a.m. 10 00 a.m. 4 25 p.m.	10 45 a.m. 10 27 a.m. 5 00 p.m.	10 50 a.m. 10 33 a.m. 5 06 p.m.	4 5 4 6 4 1 4 5	50 6 49 4 48 1 47 2	114 8 120 4 108 7 110 0	2,415 2,300 2 550 2,520
			Average	4 4	48 8	113 5	2,445

TABLE 2—Continued

Case	Date	Time			Millions of red cells per cu mm of venous blood in		Cc of cells per 100 cc of venous blood in		Per cent of concen tration of dye* in plasma in the venous blood of		Plasma volume on the basis of the dye concentration in the venous blood of		
		Of assuming position	Of dye injection	Of observation	Right arm	Left arm	Right arm	Left arm	Right arm	Left arm	Right arm	Left arm	
					Foot	Foot	Foot	Foot	Foot	Foot	Foot	Foot	
Walking†††													
October 31, 1926		9 30 a m	9 32 a m	9 36 a m 9 37½ a m	4 2	4 4	45 7	45 9	98 3	98 1	2,820	2,825	
		Average			4 3		45 8		98 2		2,820		
		has subsequently been assumed to represent 100 per cent concentra-											

580

- * In cases 1 to 6, the average plasma volume for the horizontal position has arbitrarily been assumed to represent 100 per cent concentration of dye
- ** The first row of figures is for the horizontal position and the second row for the standing still position
- *** The figures of April 11, 1927 have been included in the averages
- † In this and table 3, the average dye concentration and plasma volume figures for the standing still position include only those determinations on foot venous blood which were made after dye mixing had become complete.
- †† Had breakfast at 5 a m and a light lunch at 10 a m.
- ††† The injection of the dye was immediately preceded by a rest of about 45 minutes in the horizontal position

Interrelation of the various manifestations of the plasma volume reduction

Assuming that the fluid lost from plasma in a subject in the standing still position is protein free, the changes in red count, plasma protein and plasma water calculated from the changes in total plasma volume correspond well with the actual observations (table 5). Moreover, the total cell volume for each subject, calculated from the total plasma

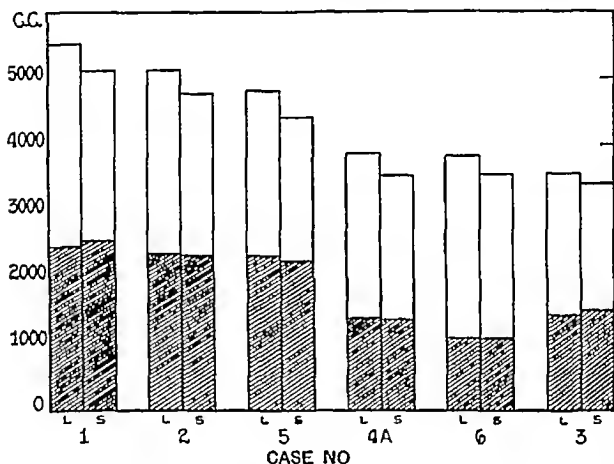


FIG 2 THE CONSTANCY OF THE TOTAL CELL VOLUME IN THE RECUMBENT AND STANDING STILL POSITIONS (TABLE 6)

Cross-hatched areas denote total cell volume, and white areas, total plasma volume. "L" denotes the recumbent and "S" the standing still position

volume and the cell percentage, is the same in both the recumbent and standing still positions (table 6, figure 2)

The reciprocal relation between the protein and water changes is shown in figure 3

These facts are consistent with the hypothesis that there has been, on the average, a net loss of 110 cc of a protein free fluid per liter of plasma, or a total loss of 290 cc, (table 1, column III), and no other change

TABLE 3

Detailed figures showing the effect of posture upon the composition and volume of the blood and upon the mixing of the dye (cases 3 to 6)

Case	Date	Time		Of dye injection	Of observation	Millions of red cells per cu mm of venous blood in		Cc. of cells per 100 cc. of venous blood in		Per cent concn of dye* in plasma in the venous blood of		Plasma volume on the basis of the dye concn in the venous blood of		Plasma (arm venous blood)			Total CO ₂ (arm venous blood)			
		Right arm	Left arm			Right arm	Left arm	Right arm	Left arm	Right arm	Left arm	Foot	Right arm	Left arm	Foot	Protein		Water	Chloride as NaCl	Specific gravity
Horizontal																				
3 N C	October 28, 1926	9 30 a m	11 30 a m		11 35 a m	4 2		39 9		96 5		2 220		7 591 0	613	1 027	63 2	53 6		
	November 8, 1926	10 00 a m.	12 00 p m		12 06 p m	4 3 4 1	40 3	39 7	101 0	100 0		2 120 2 140		6 891 2	588	1 025	62 9	51 2		
	November 30, 1926	10 00 a m	12 30 p m.		12 36 p m	4 1	40 0		99 1			2 160								
	January 17, 1927	9 00 a m	1 00 p m.		1 05 p m.	40 5	40 5		97 1			2 205								
	January 31, 1927	10 00 a m.	1 00 p m		1 04 p m	4 2	40 8		101 1			2 115								
	March 7, 1927	10 00 a m	12 30 p m		12 36 p m.	4 1	39 3 41 4	40 9	106 0	102 1	107 2	2 020 2 095 1 995								
	April 18, 1927	9 30 a m	12 30 p m		12 35 p m	3 9	38 1		97 1			2 205								
	May 10 1927	10 00 a m	12 00 p m		12 06 p m	4 1	40 3		98 2			2 180								
							39 7	40 1	101 5	98 7	104 5	2 110 2 170 2 050								
			Averages****			4 1	40 1		100 1			2 140		7 291 1	600	1 026	63 1	53 9		
Standing still																				
	October 30, 1926	11 15 a m	12 00 p m		12 07 p m	4 5 4 4	43 9	43 3	109 4	111 4		1 955 1 920		90 5	591	1 030	58 3	49 8		
	November 16, 1926 December 20 1926	11 45 a m	12 30 p m		12 08 p m	4 6	5 1	43 5	45 1	111 1		2 115		8 190 4	591	1 028	63 3	55 8		
		11 00 a m	12 00 p m		12 37 p m	4 5	43 0	44 3	116 2	115 3		1 840 1 855		8 590 4	575	1 028	63 8	55 5		
					12 05 p m															
				Averages****			4 5 4 4 8	43 5	43 8 45 5	112 2	113 3		1 905 1 890							
						4 6	44 2		112 7			1 900		8 390 4	586	1 029	61 8	53 7		

[illegible]

	January 3 1927	12 00 p.m.	11 59 a.m.	12 04 p.m.	4 1	40 7	100 8	2 125	
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4A M F	November 12 1926		12 30 p.m.		12 35 p.m.		35 0 37 0		102 0 101 3		2 415 2 460		91 6		611		1 027		59 7		52 8	
	December 31 1926		12 40 p.m.		12 45 p.m.		34 8		96 8		2 580		6 9 91 3		607		1 025					
					</																	

[illegible]

5		9 30 a.m.	11 00 a.m.	11 05 a.m.	4 65 1	48 1 47 8	93 5 101 0	2 680 2 480	6 7 92 1	591 1 027	65 3 55 0
E. R. J	November 13 1926	10 00 a.m.	11 00 a.m.	11 01 a.m.	4 7	47 3 47 1	99 3 99 9	2 523 2 510	7 3 91 7	604 1 023	
	December 18, 1926	8 30 a.m.	10 30 a.m.	10 35 a.m.	4 5	49 9 48 1 49 1	104 9 100 7	2 390 2 490			
	March 12 1927	9 00 a.m.	10 30 a.m.	10 36 a.m.	4 6	47 6	102 8	2 440			
	April 23 1927	8 00 a.m.	10 00 a.m.	10 05 a.m.	4 9	47 5	99 3	2 525			
	May 27 1927										
Averages					4 7	48 0	100 2	2 505	7 0 91 9	598 1 025	65 3 55 0

TABLE 3—Continued

TABLE 3-Continued

Case	Date	Time		Of dye injection	Of observation	Millions of red cells per cu mm of venous blood in		Cc. of cells per 100 cc of venous blood in		Per cent concn of dye* in plasma in the venous blood of		Plasma volume on the basis of the dye concn in the venous blood of		Plasma (arm venous blood)			Total CO ₂ (arm venous blood)				
						Right arm	Left arm	Right arm	Left arm	Right arm	Left arm	Right arm	Left arm	Foot	Protein	Water	Chlorides as NaCl	Specific gravity			
		Of assuming position																		Plasma	Whole blood
6 F G B ††††	November 20, 1926††† February 12, 1927	Averages****				5 1	5 1	50 9	116 0	121 4	113 7	2 065	2 205	98 0	8 290	7 491	556	1 029	73 4	60 8	55 3
						5 0 5	4 8	51 5	51 1	7 113	5 115	2 210	2 170	2 660	8 290	7 491	617	1 029	59 3	49 7	
						4 8	4 8	50 5	49 8	7 113	5 115	2 210	2 170	2 660	8 290	7 491	617	1 029	59 3	49 7	
						5 1	5 1	50 9	116 0	121 4	113 7	2 065	2 205	98 0	8 290	7 491	556	1 029	73 4	60 8	55 3
						5 1	5 1	50 9	116 0	121 4	113 7	2 065	2 205	98 0	8 290	7 491	556	1 029	73 4	60 8	55 3
6 F G B ††††	December 20, 1926 January 3, 1927 June 11, 1927	Averages				4 1	4 1	28 1	100 0	99 5	100 1	2 770	2 750	100 0	6 491	6 591	606	1 028			
						4 1	4 1	28 8	100 2	99 5	100 1	2 770	2 750	100 2	6 491	6 591	605	1 027			
						4 2	4 2	28 1	100 2	99 5	100 1	2 770	2 750	100 2	6 491	6 591	605	1 027			
						4 1	4 1	27 7	100 2	99 5	100 1	2 770	2 750	100 2	6 491	6 591	605	1 027			
						4 1	4 1	28 1	100 0	99 5	100 1	2 770	2 750	100 0	6 491	6 591	606	1 028			
6 F G B ††††	December 27, 1926 January 22, 1927	Averages				4 6	4 6	30 2	110 9	108 5	113 0	2 540	2 440	110 9	7 990	7 990	615	1 029			
						4 7	4 7	29 9	111 1	108 5	113 0	2 540	2 440	111 1	7 990	7 990	615	1 029			
						4 5	4 5	30 3	111 1	108 5	113 0	2 540	2 440	111 1	7 990	7 990	615	1 029			
						4 6	4 6	30 2	110 9	108 5	113 0	2 540	2 440	110 9	7 990	7 990	615	1 029			
						4 6	4 6	30 2	110 9	108 5	113 0	2 540	2 440	110 9	7 990	7 990	615	1 029			

* See first footnote to table 2

** See second footnote to table 2

*** The figures of April 7, 1927 for the horizontal position have been included in the average figures for this position

**** See fourth footnote to table 2

† The injection of the dye was immediately preceded by a rest of about 2 hours in the horizontal position

†† The dye was injected into a right foot vein instead of into an arm vein The injection time was much prolonged because of the force required to inject the dye.

††† Had to sit down during dye injection and mixing because of faintness Blood for protein, water, chloride and CO₂ was taken just before sitting down

†††† The cell volume for this subject, though low, has remained unchanged for 2 years, in spite of the constant administration of thyroid extract

It is of interest that L J Henderson (13) has recently calculated that the concentration changes in exercise reported by Bock et al (14) could be accounted for by the removal from blood of 50 cc per liter of a fluid of the composition of lymph (protein free) and the addition to it of 25 cc of cells per liter. A loss of 50 cc of fluid per liter of blood is roughly equal to a loss of 90 to 100 cc per liter of plasma. Thus it would appear that the blood loses approximately the same amount and type of fluid when a subject exercises as when he stands still.

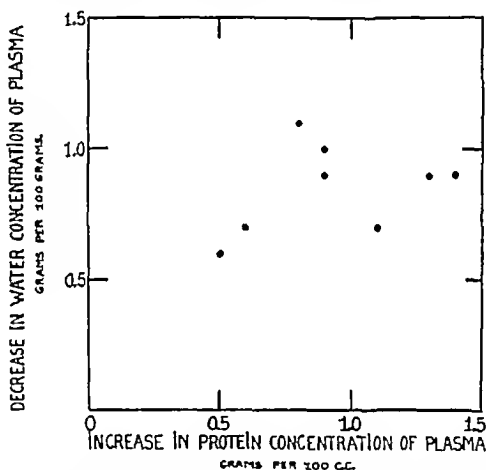


FIG 3 INCREASE IN PLASMA PROTEIN CONCENTRATION AND DECREASE IN PLASMA WATER CONCENTRATION ACCOMPANYING CHANGE FROM THE RECURRENT TO THE STANDING STILL POSITION (TABLE 1)

The rate at which the loss of plasma water occurs

The data on cases 1, 4b, and 9 indicate that the concentration changes reach a maximum after standing still 20 to 30 minutes. The data on case 1 are especially interesting in this respect. Numerous observations on this case during a period of 3 months yield uniform measurements of cell volume in both arm and foot venous blood in the horizontal position. On the same individual many other observations

TABLE 4
Observations on the same day on the same individual, first lying down, then standing still and then lying down again (cases 7, 8, 4b and 9)

Case	Date	Observation number	Position	Time		Plasma			Remarks
				Of assuming position	Of observation	Protein	Water	Chloride as NaCl	
7 P K T	April 1, 1927	1	Horizontal	9 55 a m	11 34 a m	gm / 100 cc	grams / 100	mgm / 100 cc	Following 3rd observation, became pale, nauseated and dizzy and had to lie down. Stood up again at 12 28 p m. Could not continue standing because of faintness, so resumed horizontal position at 12 35 p m.
		2	Horizontal	9 55 a m	11 53 a m	6.0	92.3	616	
		3	Standing still	11 57 a m	12 22 p m	6.2	92.2	614	
		4	Horizontal	12 35 p m	12 44 p m	7.0	91.3	616	
		5	Horizontal	12 35 p m	1 30 p m	6.7	91.9	617	
			Average for horizontal position			6.0	92.2	620	
8 W O T	March 24, 1927		Average for standing still position			6.1	92.2	617	Following 3rd observation, had to lie down about 3 minutes because of cold sweat, faintness and nausea.
		1	Horizontal	8 35 a m	9 05 a m	7.0	91.4	592	
		2	Horizontal	8 35 a m	9 20 a m.	7.0		595	
		3	Standing still	9 25 a m	9 50 a m	7.3		594	
		4	Standing still	9 54 a m	10 12 a m	7.5	90.7	589	
		5	Horizontal	10 13 a m	10 42 a m	7.2	90.8	589	
4b M T	April 8, 1927	6	Horizontal	10 13 a m	11 25 a m	7.1	91.1	594	
			Average for horizontal position			7.0	91.3	594	
			Average for standing still position			7.5	90.7	589	
		1	Horizontal	10 37 a m	11 37 a m	7.5	90.8	603	
		2	Horizontal	10 37 a m	11 57 a m	7.1	91.1	605	
		3	Standing still	12 03 p m	12 32 p m	7.7	90.7	605	
		4	Standing still	12 03 p m	1 02 p m	7.8	90.5	605	
		5	Horizontal	1 03 p m	1 30 p m	7.0	91.3	605	
		6	Horizontal	1 03 p m	1 59 p m	7.1	91.6	611	
			Average for horizontal position			7.2	91.2	607	
			Average for standing still position			7.8	90.5	605	

9 J C	March 17, 1927	1	Horizontal	8 00 a.m.	9 30 a.m.	7 4	90 9	594
		2	Horizontal	8 00 a.m.	9 45 a.m.	7 4	90 9	595
		3	Standing still	9 50 a.m.	10 15 a.m.	8 3	89 9	578
		4	Standing still	9 50 a.m.	10 50 a.m.	8 1	90 0	584
		5	Horizontal	10 50 a.m.	11 25 a.m.	7 7	90 3	595
		6	Horizontal	10 50 a.m.	12 00 m.	7 2	91 1	592
		Average for horizontal position				7 3	91 0	594
		Average for standing still position				8 2	90 0	581

were made at different times after standing still. These are plotted in figure 4. Several measurements of cell volume have also been made on this subject on the same day at different intervals after assuming the standing still position. These are plotted in figure 5. It will be observed that, on standing still, there is a rapid increase during about 20 minutes, after which the rate of increase diminishes up to about 30 minutes, when a level is reached. This curve is of the type to be expected and, except that the increase occurs much more slowly,

TABLE 5

Comparison of the values observed for the red count, plasma protein and plasma water with those calculated from the changes in total plasma volume

Case	Average red count for the standing still position			Average plasma protein for the standing still position			Average plasma water for the standing still position		
	Observed	Calculated from change in total blood volume	Ratio—observed/calculated	Observed	Calculated from change in plasma volume	Ratio—observed/calculated	Observed	Calculated from change in plasma volume	Ratio—observed/calculated
	millions per cu mm	millions per cu mm		per cent	per cent		per cent	per cent	
1	5.7	5.2	1.10						
2	4.4	4.7	0.94						
3	4.6	4.3	1.07	8.3	8.1	1.02	93.0	92.7	1.002
4a	4.3	4.3	1.00	8.2	7.9	1.04	93.0	93.0	1.000
5	5.1	5.1	1.00	7.8	8.1	0.96	93.4	93.3	1.001
6	4.6	4.4	1.04	7.9	7.2	1.10	93.0	93.2	0.998
Average	4.8	4.7	1.025	8.1	7.8	1.03	93.1	93.1	1.000

is similar to that reported by Bohme (4) for the increase in protein concentration during exercise.

There are insufficient data to determine when dilution of the blood becomes complete on reverting from the standing still to the horizontal position. In case 7 the plasma water had not reached its prestanding level within 9 minutes. In cases 8 and 4b, the plasma water had increased as much at the end of 25 to 30 minutes as at the end of an hour. In case 9, however, the process appeared to be still incomplete at the end of 30 minutes but had reached or passed the prestanding level at the end of an hour. Since this subject had untreated myx-

dema, the data suggest that this slow dilution may have been due to a diminished rate of absorption of water from tissues. In such cases, blood flow is known to be slow (15)

Differences between the relative cell volume of arm and foot venous blood in the standing still position

A review of the data shows that in nearly every instance where samples of blood were simultaneously taken from both arms and a

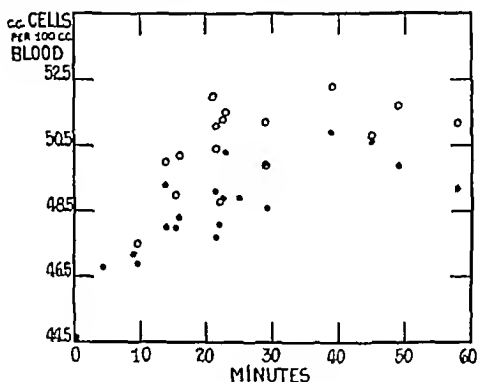


FIG 4 THE RATE AT WHICH THE RELATIVE CELL VOLUME INCREASES ON CHANGING FROM THE RECUMBENT TO THE STANDING STILL POSITION (CASE 1, TABLE 2)

Three observations are included that are not recorded in the table. Average of observations on arm venous blood represented by dots. Observations on foot venous blood represented by circles

foot when the subject was standing still, the relative cell volume was the same in the venous blood of the two arms, but greater in the venous blood of the foot (table 7). In the horizontal posture, however, the volumes were the same in all three places

Such variations may be due to

- 1 Greater filtering off of fluid from the foot capillaries than from the capillaries of the hands and arms

- 2 A sedimentation of red blood cells in the blood vessels of the foot due to marked slowing of the circulation
- 3 In part to greater CO_2 content of foot venous blood than of arm venous blood resulting in swelling of the red blood corpuscles in the former

The differences in CO_2 content are certainly not great enough to produce the differences in cell volume observed. Therefore, the first two possibilities seem to be the most likely ones, and, of these, the first seems to be more probable than the second, although a combination of all three factors may be at work.

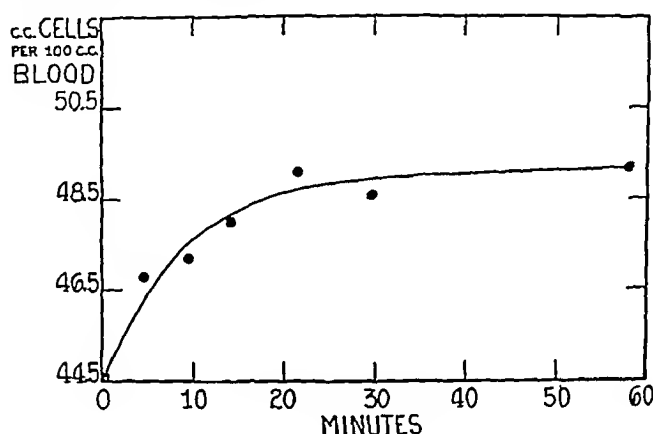


FIG 5 THE RATE AT WHICH THE RELATIVE CELL VOLUME INCREASES ON CHANGING FROM THE RECUMBENT TO THE STANDING STILL POSITION (ARM VENOUS BLOOD ONLY)

All observations recorded were made on case 1 on the same day, in contrast to those in figure 4 which were made on different days over a period of months. Note that the rate at which the change occurs is about the same in both figures.

Along with the greater venous pressure in the foot in the standing still position (16) (17) (18), an actual increase in the filtering off of water from plasma in foot capillaries as compared with that in arm capillaries would be expected.

Effect of posture on the mixing of the dye

The more dilute the dye in any given sample of blood, the greater the plasma volume calculated therefrom. For the sake of convenience in interpreting the data, we have expressed the plasma volumes not

only in cubic centimeters but also in percentages of dye concentration, arbitrarily taking the dye concentration corresponding to the average plasma volume for each subject in the horizontal position as a standard of comparison (100 per cent). Thus, for example, if (case 1) the average total plasma volume of 3055 cc., for the horizontal position,

TABLE 6

The total cell volume remains constant when the subject changes from the recumbent to the standing still position

Case	Cc. of cells per 100 cc. of blood		Total plasma volume by dye method (cc.)			Calculated total blood volume (cc.)			Total cell volume (cc.)		
	Lying	Standing	Lying	Standing	Difference	Lying	Standing	Difference	Lying	Standing	Difference
1	44.6	49.6	3,055	2,580	-475	5,520	5,120	-400	2,465	2,510	+75
2	45.9	48.8	2,775	2,445	-330	5,130	4,780	-350	2,355	2,335	-20
3	40.1	44.2	2,140	1,900	-240	3,575	3,405	-170	1,430	1,505	+75
4a	35.6	38.1	2,495	2,195	-300	3,880	3,550	-330	1,385	1,355	-30
5	48.0	50.9	2,505	2,165	-340	4,820	4,410	-410	2,315	2,245	-70
6	28.1	30.2	2,755	2,485	-270	3,835	3,560	-275	1,080	1,075	-5
Average					-325			-320			+5

TABLE 7

The effect of posture upon the volume of cells in blood simultaneously withdrawn from right arm, left arm and foot veins

Case number	Cc. of cells per 100 cc. of venous blood					
	Lying down			Standing still		
	Right arm	Left arm	Foot	Right arm	Left arm	Foot
1	44.6	44.7	44.5	49.0	49.1	50.6
3	39.4	40.8	40.6	43.5	43.8	45.5
5	49.9	48.1	49.1	50.5	49.8	51.7
Average	44.6	44.5	44.7	47.7	47.6	49.3

be assumed to correspond to 100 per cent dye concentration, then obviously a plasma volume of 2580 cc. (the average volume for the standing still position) corresponds to a dye concentration of $\left(\frac{100 \times 3055}{2580}\right)$ per cent = 118.3 per cent

The dye mixing data on cases 1, 3 and 5 (particularly case 1) show two significant things

- 1 A much longer time is required for the dye concentration in the blood to become uniform all over the body in the standing still position than in the recumbent position ⁴

- 2 When the concentration has become uniform, it is greater in the standing still position than in the recumbent position

Most of the delay in mixing in the standing still position appears to be due to a marked slowing of the circulation in the lower extremities. It may be seen from the data on cases 1 and 3 (table 2, e g, experiment of June 9, 1927 on case 1) that, after a mixing time of 5 to 6 minutes, the dye concentration was the same in the venous blood of the right arm, of the left arm and of a foot when the subject was in the recumbent position. Complete mixing of the dye with the blood may, therefore, be fairly assumed at this time ⁵. In the standing still position, however, a different situation exists. As cases 1, 3 and 5 show (particularly case 1, table 2, e g, experiment of July 14, 1927) $5\frac{1}{2}$ to 8 minutes after injection, the dye concentration in foot venous blood was invariably less than in arm venous blood although the concentration in both arms was the same. After a time, which in case 1 varied from 9 to $14\frac{1}{2}$ minutes, the dye concentration in the foot slowly increased until it became the same as in the arms or even slightly greater ⁶. Curiously enough, however, the concentration in the arms, in the meantime, did not decrease or decreased only slightly. This observation has since been corroborated

⁴ It has also been shown that a much longer time elapses in the standing still than in the recumbent position, before dye injected into an arm vein appears in a foot vein and vice versa (19)

⁵ It should be emphasized that 5-6 minutes does not necessarily represent the minimum time required for mixing to become complete when the subject is in the horizontal position

⁶ Thus, in case 1, it took at least 2-3 times longer in the standing still than in the recumbent position for the dye concentration in the feet to become as great as that in the arms. Judging from the average figures of Turner (20) and of Field and Bock (6), the cardiac output in this case was probably reduced 20-50 per cent. Thus the slowing of the circulation in the lower extremities in the standing still position is probably not exclusively due to the reduced output of the heart

by several observations on another subject. It appears to represent a definite phenomenon the explanation of which is at present obscure.

The greater dye concentration in the standing still position after complete mixing is illustrated by numerous experiments on different days on case 1 (tables 2 and 8) and a smaller number on case 3. The experiment in which samples were taken on subject 1 in the recumbent and then in the standing still position on the same day, after a single dye injection, is further proof of the same phenomenon. On April 11, 1927, after the subject had remained two hours in the recumbent position, dye was injected in a right arm vein as usual and 8 minutes thereafter, venous blood samples taken simultaneously from right arm, left arm and left foot. In all three samples, the dye concentration was the same. The man then began standing still. Twenty-two

TABLE 8

Effect of posture upon the concentration of intravenously injected brilliant violet red (case 1)

Position of body	Average concentration of dye in plasma after complete mixing		
	Right arm venous blood	Left arm, venous blood	Foot, venous blood
Lying down	101	100	100
Standing still	119	117	120

minutes later blood samples were taken from the same three veins. In all three, the dye concentration was approximately the same, but was definitely greater (9 to 18 per cent) than in the same veins when the subject was lying down. Associated with the increase in dye concentration, was an increase in relative cell volume. This increase in dye concentration could not have occurred unless some fluid had disappeared from plasma.

Another observation worthy of note is that after complete mixing in the standing still position, the dye concentration in foot venous blood often appears to be slightly greater than in arm venous blood, whereas it is the same in all three places in the horizontal position. This is shown by the experiments of April 11, April 21, June 7 and of July 14 on case 1. The differences are not great and are within the error of the method. They are suggestive, however, and consistent with

the hypothesis of a slightly greater filtering off of plasma water from the capillaries of the foot than from those of the arm

If the subject walked during the time that elapsed between the moment of dye injection and that of collection of blood for the plasma volume observation, the concentration of dye in arm venous blood was the same as it was when the subject was in the recumbent position, provided the injection of the dye had been immediately preceded by a rest period in this position (See experiment of October 31, 1926 on case 2, and of January 3, 1927 on case 3) There is some reason to suppose, however, that, after a longer period of walking about, there may be a loss of water from the plasma (4) Therefore, since in the recumbent position, the circulation is least affected by gravity and the dye readily becomes uniformly distributed throughout the plasma, this position would appear to be the one of choice for blood volume and other comparative blood studies

In all plasma volume observations, the rate at which dye disappears from the circulation is very important It might be supposed that, after mixing had become complete while the subject was in the standing still position, the amount of dye left in plasma would be appreciably less than that injected For this reason it might appear that the observed plasma volume, while less than that for the horizontal position, would be higher than it really was One of us (3) has noted, however, that after repeated plasma volume observations, within a short period of time on the same individual, the rate at which the dye leaves the circulation decreases markedly, contrary to Lindhard's observation Thus, after an hour under these conditions, the dye may be just as concentrated as after 5 minutes and 1 week or 10 days after the last of a series of 3 or 4 plasma volume observations done within 1 or 2 days of one another, the plasma may still be well tinged with dye (not sufficiently, however, to cause an appreciable error in the method) Illustrations of the slow disappearance of dye from plasma following repeated dye injections, may be seen in the data of March 31, April 21, June 7 and June 16 on case 1

Following a single dye injection, or a month or longer after repeated injections, however, the dye leaves the circulation at a more rapid rate so that dye disappearance may mask the volume reduction which occurs in the standing still position This was probably the case in the

lying-followed by-standing experiment of April 7, 1927 on case 3. This was similar to the experiment of April 11, 1927 on case 1 described above. One month had elapsed, however, since any observations had been made on the subject. Thus, while the cell volume rose when the standing still position was assumed, after complete dye mixing had occurred in the recumbent position, the dye concentration remained about the same or increased only slightly.

Total CO₂

Total CO₂ determinations were made on plasma and whole blood in a few cases. They showed no significant variations—except in case 5 on November 20, 1926 when, just preceding an attack of syncope in the standing still position, there was a well marked rise in CO₂ with a proportional drop in chloride.

Chlorides

The chlorides were irregular, no significant change being recorded except the one just noted.

DISCUSSION

In an effort to elaborate their significance, our findings are correlated with some of those in the literature which have a bearing on this subject.

Evidence to show that in the standing still position blood collects in dependent portions of the body

Piorry (21) in 1826 was one of the first to comment on the marked impediment to the circulation in the erect posture. He attributed this to the influence of gravity and stated that it is due to this cause that the veins and capillaries of the hands become filled if the arms are held down. For the same reason varices and varicocoeles enlarge when a person stands, and diminish when he lies down, and the head and face become red when held down. He opposed Bichat's teaching that in syncope the heart's activity is suspended, claiming that the heart continues to beat but that the beats have not force enough to overcome the effect of gravity. "It is not marvelous. It is simple

There is no doubt that it is the absence or presence of blood in the vessels of the brain that causes or dispels syncope " Piorry corroborated his hypothesis by showing that the horizontal position immediately restored consciousness in humans who had fainted and in dogs who had been bled in the "vertical feet down" position until syncope supervened

Salathé (22) in 1877 made the significant observation that centrifugal force was just as effective in causing the death of rabbits as the "vertical feet down" position

The influence of gravity on the distribution of blood is well shown by the simple experiment of Stephens (23) in 1904 In 21 healthy male medical students, he not only found that the systolic pressure in the radial arteries invariably dropped on changing from the horizontal to the upright position but also observed that in the lateral position the radial artery pressure in the arm which was uppermost was always decidedly less

In 1895 Leonard Hill (24) reported that in cats, dogs and monkeys in the "vertical feet down" position the pressures in the femoral artery and vein rose while the carotid artery and jugular vein pressures fell markedly The reverse effects were observed in the "vertical head down" position

Through the open chest wall of an animal in the "vertical feet down" position, he frequently observed complete emptying of the heart, particularly if the splanchnics had been eliminated This was accompanied by a fall in intracranial pressure, a marked drop in systolic pressure in the carotid, and finally by the cessation of respirations and of the pulse and by the apparent death of the animal The heart continued to contract rhythmically "On turning the animal to the horizontal position, the heart is seen to fill again immediately The blood is actually shot out of the vena cava and from the veins of the splanchnic area into the heart "

Field and Bock (6) found that in 10 normal but non-athletic individuals "the average rate of blood flow (cardiac output) while sitting was 76 per cent and while standing 50 per cent of the rate while reclining Inasmuch as the pulse rate increased from an average of 63 per minute in the reclining position to 65 per minute in the sitting position and 90 per minute in the standing position, the output per beat was tremendously diminished in the upright posture

Turner (20), using the same method on women, and Lindhard (25), Collett and Liljestrand (26) and Henderson and Haggard (27), using different methods, have reported findings which corroborate those of Field and Bock.

Although Salathé (22) in 1877 showed that rabbits died in the course of 15 minutes to 2 hours in the "vertical feet down" position, it remained for Churchill, Hurxthal and Miller (28) to prove that this was due to a markedly diminished cardiac output.

In view of the blood flow work just reported it is easy to understand the marked drop in pulse pressure (6) (20) (29) and in the pressure in the pulmonary artery (28) that occur in the motionless upright position.

The increase in venous and capillary pressures in dependent parts of the body in the standing still position

Associated with the collection of blood in dependent parts of the body when standing still there occurs an increase in venous pressure. This is obvious from the marked venous distension in the hand held down vertically or in the foot of a standing individual compared with the virtual collapse of such veins when held at heart level. The veins of the lower extremities in a subject standing still slowly become markedly engorged and the feet become cold and of a reddish blue color. No suction is required to withdraw blood from such a foot vein; the venous pressure squeezes the syringe piston out. On the contrary great difficulty is experienced even in puncturing the same vein when the subject is in the horizontal position, and, in many instances, once the vein is punctured the blood flows extremely slowly.

A similar observation was made by Leonard Hill (24). He noted that while a marked increase in venous pressure in the femoral vein occurred in animals in the "vertical feet down" position, the pressure became negative in the jugular vein and no blood would flow from a puncture hole. The reverse was true in the "vertical head down" position.

Recklinghausen (16) found that when the arm of a woman was held down vertically, the pressure in a hand vein was 40 cm. of water as compared with a pressure of 10 cm. of water when the arm was held at heart level. In a foot vein of the same woman the pressure was 62

cm of water in the sitting position and 79 cm of water in the standing position, pressures just about sufficient to support columns of blood reaching to the symphysis and not to the heart. Similar findings have been reported by Hooker (18) and by Carrier and Rehberg (17). The foot veins fill only slowly, however, in the erect posture and Recklinghausen states that he might perhaps have observed a further rise in venous pressure had he followed it over a long enough period. He was inclined to attribute the relatively small change in foot venous pressure as compared with arm venous pressure to a marked increase in vasomotor tone in the lower extremities in the erect posture causing the blood to trickle through very slowly to the venous side.

Resulting at least in part from the increased venous pressure in dependent parts of the body when a person stands still, there appears to be an increase in capillary pressure. Recklinghausen (16) showed that the capillary pressure was much greater in the foot of a standing woman and also in her hand when her arm was held down vertically than in the same parts of the body at heart level. The increase in capillary pressure in the foot, however, while absolutely greater, was relatively less than in the arm. Carrier and Rehberg (17), using a more accurate method, have shown that in the hand, the capillary pressure varies with the venous pressure. It is greatest when the hand is held down vertically and decreases until a level is reached as the hand is raised above the heart.

The marked increase in capillary pressure in the lower extremities of a person standing still, is obvious from a very simple experiment. A small needle prick which, in the skin of a foot of a person in the horizontal position, will occasion no bleeding, in the standing still position will cause oozing of blood for several minutes.

Effect of increased venous pressure on the composition of the blood

Cohnheim (30) was one of the first to show that, as a result of venous stasis due to application of a tourniquet, a fluid poor in protein passes very freely out of the capillaries into the tissues and from there into the lymph stream so that the small veins and capillaries became distended with erythrocytes. It has been shown that, under these circumstances, there is an increase in hemoglobin concentration, red count, specific gravity and in the dry weight of whole venous blood in

the area distal to the tourniquet (31) (32) An increase in total plasma protein in the same area has been reported by several observers (4) (33) (34) (35) (36)

Drury and Jones (37) have recently shown, by plethysmographic studies, that edema is produced in the legs of healthy men as a result of raising the venous pressure by inflation of a blood pressure cuff The rate of formation of edema appeared to depend upon the height to which the venous pressure was raised Increase in volume due to increase in blood alone was allowed for

It would seem inevitable that, when a person stands still, the capillary pressure should increase most in the lowermost parts of the body The arterial pressure while dropping in the brachials and carotids in animals in the "vertical feet down" position increases in the femorals, both changes being due to gravity Thus the capillary pressure in the legs is probably augmented from both the arterial and venous sides (the venous pressure being, of course, the more important) and the conditions favor the squeezing out of fluid from the plasma into the tissues

From our observations, it is obvious that the fluid lost from plasma in the standing still position remains somewhere within the body From the considerations just presented of the physical conditions involved, it would appear probable that most of it is collected as lymph in the lower extremities This assumption is supported by the observation of Field and Bock (6) "We have noted that while a subject was standing during an experiment the calves of his legs became indurated and brawny and increased in circumference 1.5 cm " It is also upheld by the work of Mosso (38) Using a delicate balance board, he found that when a subject assumed the horizontal position after standing for some time, the weight of the feet end of the board only very slowly decreased, in spite of the fact that presumably the excess blood leaves the lower extremities almost immediately

Cardiac edema and the reduction in plasma water

The diminished amount of urine passed by a normal man in the standing still position as compared with the horizontal position (39) may perhaps be related to the relative anuria of the day and the polyuria of the night noted in cardiac decompensation The collec-

tion of ankle edema during the day and its disappearance during the night's rest in bed in the early stages of cardiac edema, may well be a related phenomenon. Cardiac decompensation is a condition in which numerous observers agree that there is a well marked increase in venous pressure (40) which subsides under treatment. A markedly reduced cardiac output has been shown by Meakins, Dautrebande and Fetter (41) to occur in mitral stenosis. This is probably the case in all decompensated cardiac patients. Thus, in contrast to conditions in normal man in the recumbent position, both normal man in the standing still position and the patient with cardiac edema in the recumbent position, appear to show diminished blood flow and increased venous pressure. In the one case, the increased venous pressure is due to venous congestion caused by gravity and, in the other, to venous congestion caused by a failing heart.

One of us has observed that in well marked cardiac edema there is an increase in plasma volume (42) and in this condition many workers have noted a decrease in concentration of plasma protein. The facts just presented, however, suggest that in the early stages of cardiac decompensation, when edema is present only in the ankles, a decrease in plasma water may occur.

Evolutionary significance of circulatory changes in the standing still position

The general nature of the response of the circulation to the motionless upright position appears to be the same in all mammals, but the degree of response seems to vary according to the habitual position of the animal. Those animals in which the trunk is normally supported horizontally appear to show a much poorer adaptation to the "vertical feet down" position than those in which the trunk is normally supported vertically. Thus Hill (24) found that in monkeys on changing from the horizontal to the "vertical feet down" position, the systolic pressure in the carotid artery fell much less than in cats, dogs and rabbits. He made the deduction that adaptation to the upright position was probably most complete in man.

Our observations and those of others clearly indicate, however, that even man's adaptation to this position is not complete and the maintenance of the standing still position for more than a few minutes is extremely difficult.

The mechanism for adjustment to the standing still position appears to be an increase in vasoconstrictor tone in the dependent portions of the body (16) (24). This greatly diminishes the rate of blood flow to the venous side as manifested in our experiments by the slowness of the increase in dye concentration in foot veins. Flooding of the capillary reservoirs in the splanchnic area and lower extremities is thus prevented. Such a compensatory mechanism is only partially effective, however, for once the blood does succeed in getting through to the veins, it has difficulty in returning to the heart as manifested by the marked venous and capillary engorgement. In this way a vicious cycle is created. The blood flow is slowed not only as a result of the difficulty in returning blood to the heart but also by the compensatory mechanism itself.

Although the adjustment to the erect posture is very inadequate for standing still, it appears adequate for activity. In the movements of the daily routine, muscular contractions are constantly forcing blood back towards the heart. The intrapelvic rectal pressure, normally about 15 to 25 mm Hg, may rise on very slight exertion, such as an arm or leg movement to 80 or 100 mm Hg and, if the movement is sudden, it may rise to 150 mm Hg (43). Slight leg movements may even force the blood from the feet into the chest, and thus prevent the ill effects of the motionless upright position. Under certain conditions, however, the compensatory mechanism may prove inadequate even during activity. Thus patients often faint when they first get out of bed after a long illness. This temporary loss of vasoconstrictor tone in the splanchnic area may represent a transient reversion (from disuse) to a more primitive state.

SUMMARY AND CONCLUSIONS

In the standing still position there occurs a net loss of approximately protein free fluid from the blood. This seems to be due chiefly to an increase in capillary pressure. The loss amounts on the average to about 11 per cent of the total plasma volume, and is probably greatest where the filtration pressure is most increased, namely, in the lower extremities.

The maximum fluid loss, which occurs in the standing still position

in from 20 to 30 minutes, is made up in about the same time in the recumbent position

Observations on the mixing time of a plasma volume dye show a marked prolongation of the time required for the concentration to become uniform in the blood all over the body in the standing still position. The same data suggest that the slowing of the circulation in the lower extremities in the standing still position is greater than that in other parts of the body.

The findings recorded show the importance of a rest period in the horizontal position for making blood volume and other comparative blood studies.

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THE EFFECT OF POSTURE UPON THE VELOCITY OF BLOOD FLOW IN MAN

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INTRODUCTION

We (1) (2) have observed that a much longer time elapses in the standing still position than in the recumbent position before an intravenously injected dye attains a uniform concentration in the blood throughout the body. Measurements of the velocity of blood flow in different positions of the body have now been made by a dye method

METHOD

The experiments were done in either the morning or early afternoon, with the subjects fasting. All experiments were preceded by a rest period of at least 30 minutes in the horizontal position. When in the upright position the subjects stood with their feet about 6 inches apart and remained as motionless as possible. About 2.5 to 3.0 cc. of a 4 to 5 per cent solution of brilliant vital red was quickly injected into a cubital vein or into a foot vein (usually the internal saphenous just below the internal malleolus). This amount of dye produced a well marked coloring of the serum and its injection rarely required more than 5 seconds. In the standing still position, the arm was held horizontally when dye was injected and down by the side when blood was collected.

In order to determine the time of the appearance of dye in the venous blood of any part of the body, venous blood from that part was collected in small test tubes which were changed at 15 second

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TABLE 1

Case	Date	Position of body	Time		Site of injection	Time (seconds) that elapsed between beginning of injection and appearance of dye in			
			Of assuming position	Of dye injection		Right arm vein	Left arm vein	Right foot vein	Left foot vein
1 W M	July 11, 1927	Lying	11 30 a m	1 41 p m	Right arm vein	60-75	30-45	45-60	
	July 21, 1927	Lying	8 00 a m	10 40 a m	Right foot vein	? Trace at 45-60	60-75 ? Trace at 45-60		
	July 7, 1927	Standing still	2 04 p m	2 35 p m	Right arm vein		45-60	? slight trace at 120-135	
	July 28, 1927	Standing still	10 19 a m	10 43 a m	Left foot vein	85-100		Trace at 135-150 Trace at 160-175	
2 M L D	July 26, 1927	Lying	11 00 a m	1 07 p m	Left foot vein	30-45	30-45		? Trace at 75-90++
	August 2, 1927	Lying	12 00 m	3 00 p m	Right arm vein		30-45		at 90-105*
	July 29, 1927	Standing still	1 13 p m	1 25 p m	Left foot vein	60-75	None up to 75 but ++ at 120-135†		

3 M M	July 19 1927 July 13 1927 July 26, 1927	Lying Standing still Standing still	2 00 p.m. 2 01 p.m. 3 00 p.m.	4 12 p.m. 2 23 p.m. 3 08 p.m.	Right foot vein Right arm vein Left foot vein	40-55 None up to 75‡	55-70 15-30 (Slight) 75-90 (Trace)	None up to to 120†	
4 J G	July 15 1927	Standing still	11 25 a.m.	11 33 a.m.	Right arm vein		45-60		None up to 120‡
5 D B	July 30, 1927	Lying	10 00 a.m.	2 00 p.m.	Left foot vein	30-45 (Trace)			

* Had to keep tourniquet tightly applied to left leg in order to get any blood

† Collection of blood from left arm vein was suspended from the 75th to 120th second

‡ Had to stop collection after 120 seconds, because subject fainted

§ Subject had to sit down after 75 seconds because of weakness Fainted 15 seconds later

¶ Subject felt so faint after 120 seconds that collection had to be stopped.

intervals, starting from the time of the beginning of the injection. The blood thus collected was allowed to clot in an ice chest and was then centrifuged. The presence of dye was detected by the color of the serum.

The arm to arm circulation time for the recumbent position found by this method is longer than that reported by Blumgart and his co-workers (3). This difference can probably be accounted for by the fact that in Blumgart's method (4)

- 1 The injection time is shorter

- 2 The distance travelled is shorter (vein to artery instead of vein to vein)

- 3 The recording apparatus is sensitive enough to detect the first particle of radium C that arrives within its field, whereas in our method a small amount of dye probably appears in the blood a few seconds before its concentration becomes great enough to cause a perceptible coloring of the serum.

The method we have used is, of course, a rough one but is accurate enough to show marked changes.

EXPERIMENTAL RESULTS

The data are summarized in table 1. They show two significant things.

- 1 A much longer time is required for the dye to travel from a foot vein to an arm vein or the reverse in the standing still position than in the recumbent position.

- 2 The application of a tourniquet to a lower extremity so as to produce a moderate increase in venous pressure, when the subject is in the recumbent position, appears to be just as effective as the standing still position in prolonging the appearance time of the dye.

When the subject is in the standing still position, the dye seems to take a longer time to go from an arm vein to a foot vein than in the reverse direction. Thus in cases 1, 3 and 4, more than 120 seconds elapsed in each instance before dye injected into an arm vein appeared in a foot vein (i.e., at least twice as long as in the recumbent position, and probably longer). In cases 1 and 3, on the contrary, 85 to 100 and 75 to 90 seconds respectively elapsed before dye injected into a

foot vein appeared in an arm vein (i e , at least $1\frac{1}{2}$ times as long as in the recumbent position) This result, if corroborated by further experiments, is difficult to explain satisfactorily at present

Observations by several workers (5), (6), (7), (8), (9), have shown that, in the standing still position, blood circulates with difficulty and collects in dependent portions of the body, owing to the effect of gravity Our findings are in harmony with these observations

CONCLUSION

A much longer time is required for blood to move from an arm vein to a foot vein or the reverse when an individual is in the standing still position than when he is in the recumbent position

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THE CHLORIDE, BASE AND NITROGEN CONTENT OF GASTRIC JUICE AFTER HISTAMINE STIMULATION

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In previous papers (1) the inadequacy of the usual test meal methods of studying gastric function has been discussed. It was pointed out especially that acid titration values obtained from specimens aspirated from the stomach after a test meal varied with an unknown factor—namely, the speed of gastric emptying, and that in certain cases apparent absence of hydrochloric acid was due simply to neutralization by stomach contents. A procedure which obviated many of the variables of the older tests was introduced (2), but in order to obtain a still more accurate insight into the mechanism of gastric secretion further analysis of the constituents of the stomach juice seemed necessary. The object of the present work was to estimate, after a standard stimulus, the quantities of chloride, nitrogen and base which were secreted and to determine what, if any, aberrations from the normal occurred in cases of gastric disorder. In view of the observations of Bulger and Allen (3) presently to be discussed, it seemed of importance to find out whether deficiency of titratable acidity was due to an actual failure of chloride secretion or whether the mechanism for producing a relative deficiency of base was at fault. We also wished to determine whether any relation exists between the total amount of nitrogen in the gastric juice in health and in disease of the stomach and whether stimuli which affect acid secretion also influence the output of nitrogen.

The present report deals primarily with methods and with the findings in a miscellaneous group of hospital patients, special conditions such as "anacidity" will be discussed in future papers.

LITERATURE

Only a few thorough analyses of human gastric juice are to be found in the literature, probably because of the difficulty of obtaining satis-

factory material Carlson (4), working with people with gastric fistulae, sets down the following figures for the average composition of normal human stomach juice

Free acid	0.40-0.50	per cent
Total acid	0.45-0.60	per cent
Specific gravity	1.006-1.009	
Total nitrogen	0.051-0.075	per cent
Chlorides	0.50-0.58	per cent

These figures are in essential agreement with those of other observers

Baird, Campbell and Hern (5), and Miller and Smith (6) following Bolton and Goodhart (7) have studied the chloride content of specimens withdrawn after the fractional gruel meal used in clinical practice. The curve of chloride concentration as a rule follows that of the titratable acid at first but may continue to rise after the acid falls. This discrepancy has been interpreted as due to neutralization of acid by duodenal regurgitation or by alkaline pyloric secretion. As the analyses were not made with pure juice they are subject to all the errors which dilution by test meal introduces (1). This difficulty is avoided in the more recent observations of Berglund, Wahlquist and Sherwood (8) who examined the pure gastric juice obtained at intervals after histamine stimulation. They found a close correspondence between the curves of titratable HCl and chloride concentration and concluded that normal stomach juice contains only insignificant amounts of chlorine, if any, in other forms than hydrochloric acid. They also found an almost complete correlation between the highest chlorine figure of the gastric juice and the total base of the blood plasma.

Bulger and Allen (3) believe that chlorides are continuously secreted into the stomach at an approximately constant level and that increase in titratable acidity after stimulation is due to retention or resorption of base. This suggestion offers a further explanation for discrepancies in curves of free acid and total chlorides. As to actual determinations of base Gamble and McIver (9), working with gastric juice obtained from dogs with isolated gastric pouches, found that while the fasting juice showed an average ratio of acid (chloride) to base of 157 to 110, after a meal there was little if any increase in chloride, whereas there was a marked fall in base, the ratio then being 164 to 30. Material

obtained from an isolated pyloric pouch yielded thick viscous material with a pH of 8.4. This secretion contained chloride in about the same proportion as the fundus juice and owed its alkalinity to a much larger content of fixed base.

We have found no references to determinations of nitrogen under conditions similar to those under which our observations were made.

The volume of gastric secretion has recently been discussed by Bloomfield and Keefer (10). With regard to titratable acidity, the wide variations to be found in health and in disease are well known (11). Suffice it to say that no observations are on record in which the acidity of the gastric juice far exceeds the equivalent value of the plasma base—approximately 150 to 165 N/10 per 100 cc.

METHODS

In planning the present experiments, any procedure in which a meal was to serve as stimulus for secretion seemed unsatisfactory. One immediately introduces the complication of dilution of gastric juice by test meal, and results which express the composition of pure gastric secretion cannot be readily obtained. The following procedure was finally adopted. The subject fasted for at least twelve hours and was examined in bed under standard basal conditions. A duodenal tube was passed for a distance sufficient to allow its tip to reach the most dependent part of the stomach. The patient was urged not to swallow saliva and this point was carefully emphasized throughout the test. As soon as the tube was in place the fasting contents were withdrawn with a syringe. Continuous aspiration was then begun and the subsequent gastric secretions were collected over ten minute periods. The technique of such aspiration requires a great deal of practice if one is to approximate complete collections and avoid trauma to the stomach. One eventually develops a tactile sense which recognizes the varying phases of tone and relaxation which the fasting stomach exhibits (12). At best, collections made in this way are not invariably complete since fluid may pass out of the stomach while aspiration is being made. In the subsequent figures this reservation is implied, although the volumes are set down as total secretion for the various periods. It should also be remembered that we were working with a composite and possibly variable gastric secretion in so far as it was a mixture of juice from both fundus and pylorus. Another possible error is introduced by the presence of saliva or duodenal contents in the stomach at the beginning of the test, or by their entry into the stomach during the examination. In spite of this possibility it was decided not to lavage the stomach since this procedure in itself stimulates secretion and one cannot be sure of removing all the wash water. Bile was carefully looked for, and whenever it appeared we assumed that duodenal regurgitation had taken place. After the

fasting secretion had been collected over one or more ten-minute periods, histamine, 0.1 mgm per 10 kilos of body weight, was injected hypodermically to stimulate secretion. The aspiration was continued for as many more periods as convenient. Regurgitation of duodenal contents (bile) led to premature termination of the experiment in certain cases.

The following observations were made on the various ten-minute specimens: (1) Volume, (2) Appearance, (3) Titratable acidity, (4) Concentration of chlorine, (5) Concentration of nitrogen, (6) Concentration of base. Nitrogen was determined by Kjeldahl, chlorine by Van Slyke's method (13), and base by the method of Stadie and Ross (14). All tests were run in duplicate except in a few instances in which the amount of material was insufficient. Checks against solutions of known composition were run from time to time. As only minute amounts of phosphate are present in gastric juice (15) Stadie and Ross' method seemed suitable.

MATERIAL

Our observations are based on a study of twenty-two subjects. They were all ward patients and for the most part presented no evidence of organic disease of the stomach, although several ulcer cases were included. The clinical diagnoses are given in table 1. Volume, titratable acidity and chloride determination were made in every case, nitrogen determinations in nine cases and base determinations in nine cases. Table 2 shows a complete protocol of a single examination to illustrate the procedure, but most of the results are summarized in the following charts.

RESULTS

Volume of secretion. The total volumes of secretion per ten-minute period, in each case, before and after histamine are shown in chart 1. The figures are similar to those reported by others (16), but several points deserve comment. One is immediately impressed by the great differences in the volume of juice in different people even though the observations are made under standard conditions, the general character of the curves is, however, similar. In every case but one (no. 21) there was an increase during the first period after histamine and the output reached its maximum within twenty to thirty minutes. This tendency is well shown in the composite curve (broken line). After thirty minutes there was usually a rapid decrease in volume which at fifty to sixty minutes had fallen approximately to the pre-

histamine level The fact that the volumes of the specimens collected before histamine usually decreased requires explanation It seems certain that the passage of the tube itself acts as a transient stimulus, as this influence subsides the volumes decrease to a "basal level" Also, the first or second ten minute collection may be increased by residues of juice which were not entirely removed when the fasting contents were withdrawn

TABLE 1
Clinical diagnoses in cases which were studied

Case number	Sex	Age	Diagnosis
1	F	31	Gastric ulcer
2	F	41	Migraine
3	F	55	Post-operative myxedema (mild)
4	M	60	Embryoma of testicle
5	M	73	Chronic constipation
7	M	58	Severe anemia of long standing (not pernicious anemia)
8	M	45	Psychoneurosis
9	M	55	Gastric ulcer
11	M	32	Constipation
12	M	37	Duodenal ulcer
13	M	30	Duodenal ulcer
14	M	38	Chronic arthritis
16	M	23	Gigantism (slight)
17	M	42	Pyloric ulcer
18	M	42	Psychoneurosis
19	M	55	Duodenal ulcer
20	M	35	Duodenal ulcer
21	M	24	Psychoneurosis
22	M	40	Psychoneurosis
24	M	29	Hyperthyroidism (mild)
25	M	33	Amoebic dysentery (inactive)
27	M	65	Cancer of rectum

In a previous study (10), with alcohol as a stimulus, it was found that the ten-minute secretory volumes usually reached a maximum of not over 40 cc and practically never exceeded 60 cc It is of interest that even when one uses so powerful a stimulus as histamine a similar maximum seems to obtain It appears also, that while the absolute increase in volume is not constantly related to the abundance of

TABLE 2
Complete protocol of a typical experiment (case 20)

Number of specimen			Character	Titratable acid		Chloride			Base		Nitrogen	
	Time	Amount		Free	Total	Mgm per 100 cc.	Total for period, mgm	MEq/l	Concentration, MEq/l	Total for period, MEq/l	Mgm. per 100 cc.	Total for period
	<i>p m</i>	<i>cc</i>										<i>mgm</i>
1	1 00	60	Fasting contents Water clear—small amount of mucus	64	72	465		131 0	65 5		66 0	
2	1 00 1 10	30	Fasting contents Water clear—small amount of mucus	82	92	468	140 4	132 0	62 5	1 96	60 6	18 1
3	1 10 1 20	24	Fasting contents Water clear—small amount of mucus Histamine, 0.9 mgm	100	112	494	118 5	139 0	?	?	63 0	15 1
4	1 20 1 30	32	Water clear—some small bits of mucus	112	118	533	170 3	150 5	43 1	1 379	55 5	17 7
5	1 30 1 40	44	Water clear—some small bits of mucus	112	120	553	243 0	156 0	38 5	1 694	39 0	17 1
6	1 40 1 50	48	Water clear—some small bits of mucus	116	124	559	268 0	157 5	45 6	2 188	36 6	17 5
7	1 50 2 00	40	Water clear—some small bits of mucus	117	124	560	224 0	158 0	42 6	1 704	33 0	13 2
8	2 00 2 10	39	Water clear—some small bits of mucus	120	126	562	219 0	158 5	38 7	1 499	31 5	12 2
9	2 10 2 20	39	Water clear—some small bits of mucus	116	120	557	218 0	157 0	40 9	1 595	36 0	14 0
10	2 20 2 30		Bile									

secretion before histaminic stimulation, greater relative increases follow in cases with an initial low volume. Thus, in case 9, there was an increase from 31 to 60 cc, the volume being practically doubled by an absolute increase of 29 cc, in case 5, on the other hand, there was an increase of 19 cc to a maximum of six times the volume (4 cc) which was secreted in the period before stimulation

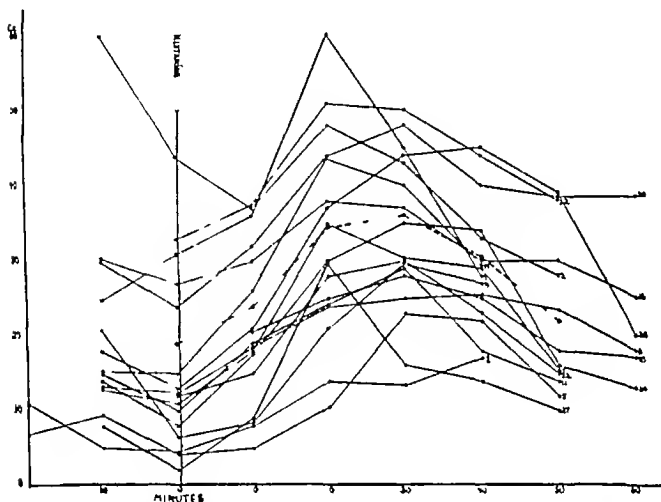


CHART 1 CURVES SHOWING VOLUME OF SECRETION FOR TEN MINUTE PERIODS BEFORE AND AFTER INJECTION OF HISTAMINE

Chlorides

Concentration of chlorides Chart 2 shows the concentration of chlorides in the various ten minute specimens from 15 cases. The general character of the curves is quite similar, beginning at a relatively low level there is a prompt rise which reaches its maximum in about twenty minutes. From this point on, the concentration remains practically constant (see composite curve—broken line). Later there is a tendency for the concentration to fall slightly. The

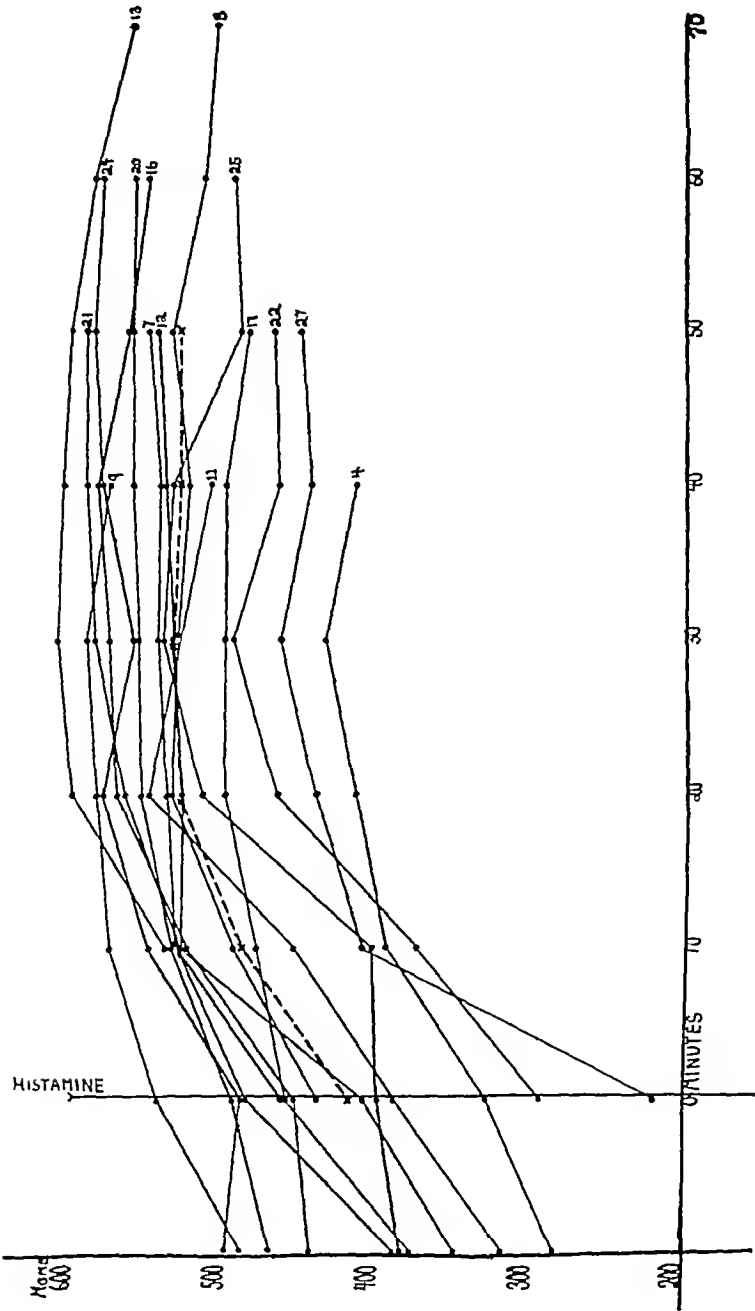


CHART 2 CHLORIDE CONCENTRATION (Mm PER 100 cc) OF GASTRIC JUICE AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

contrast, however, between the abrupt drop in volume of secretion and the sustained level of chlorides is well shown in chart 3, in which the composite graphs of charts 1 and 2 are compared. The opinion has been expressed by Bulger and Allen (3) that the stomach secretes chloride at all times in practically constant concentration. This view would not seem to be supported by the initial phases of our curves which show a steep rise. It must be recalled, however, that we were dealing with mixed gastric juice. Before histamine stimulation the volume of gastric contents was usually small and there may have been

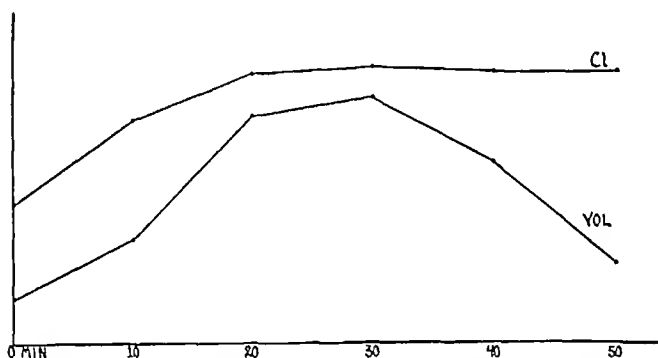


CHART 3 COMPOSITE CURVES OF VOLUME OF SECRETION AND CONCENTRATION OF CHLORIDE IN TEN MINUTE SPECIMENS OF GASTRIC JUICE

relatively large amounts of secretion from the non acid producing glands of the stomach as well as remnants of saliva, which diluted the chlorides. In case 27, for example, the specimen obtained before histamine had a chloride concentration of only 220 mgm, there were, however, only a few cubic centimeters of juice which consisted largely of mucus. Certain it is that even after the volume of secretion falls markedly the chlorides remain high (compare curves of case 24 in charts 1 and 2), and even when the secretion is still more reduced by atropin there is only a moderate fall in chlorides which again can be well explained by dilution with non-acid secretion. The observations

with atropin will be reported in another paper. On the other hand, variations in height of chloride concentration in different people clearly represent individual differences. No evidence to the contrary could be obtained from a study of other constituents of the gastric juice (nitrogen, base). Whether or not chloride always leaves the individual secreting cell at a constant concentration cannot be said,

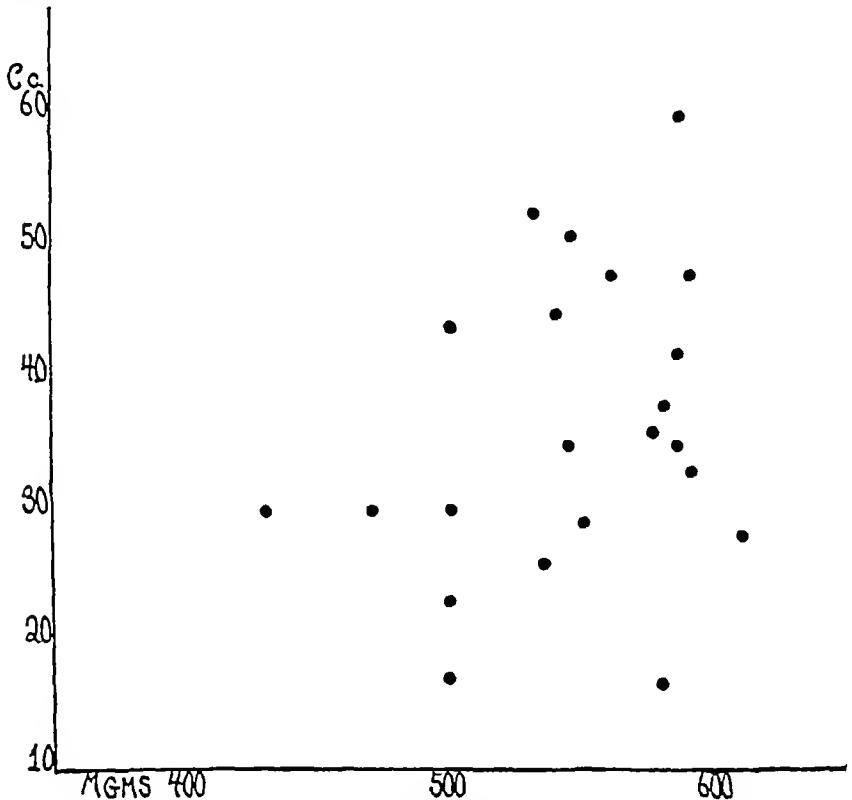


CHART 4 RELATION BETWEEN CONCENTRATION OF CHLORIDE AND VOLUME OF SECRETION OF GASTRIC JUICE

but in the juice, as poured into the stomach cavity, the differences in various people are beyond question.

In most cases a value of over 525 mgm per 100 cc was attained, the extremes being 435 mgm (case 4) and 608 mgm (case 18). As pointed out by Berglund the highest chloride figure approximates the total base of the blood plasma to which normal limits of 150 to 165

cc 0.1 N per 100 cc. have been assigned (17). Our high value of 608 mgm is equivalent to 171 cc 0.1 N per 100 cc. On the other hand, our figures are not in accord with the statement of Bulger and Allen (3) that chloride is secreted at a concentration practically equal to that of the blood

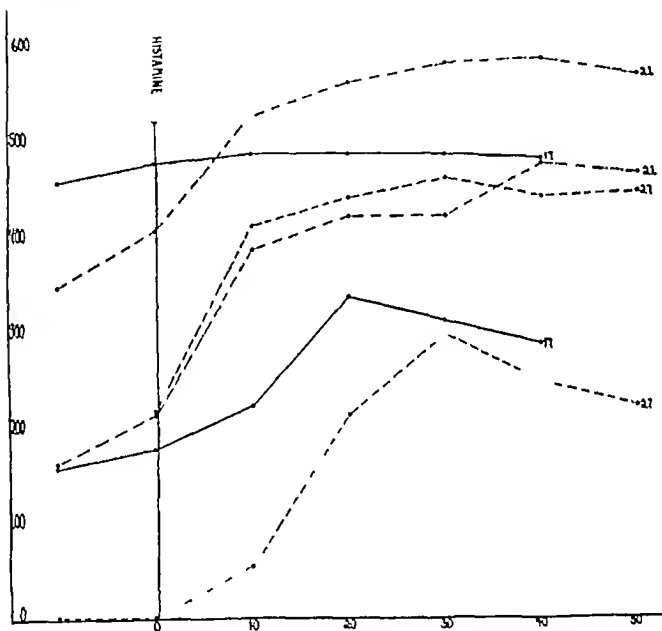


CHART 5 CURVES OF CHLORIDE CONCENTRATION DIRECTLY DETERMINED AND CALCULATED FROM TITRATABLE FREE ACID

Chart 4 shows the highest chloride concentration in various cases plotted against the volume of secretion for the corresponding period. No significant correlation can be made out, and it is evident that a large secretion implies neither high nor low chloride values except in a very general way.

A study was next made of the relation of chloride to titratable acidity¹ Much stress has been placed on this question and the general implication of the literature (5, 6, 7) is that titratable acidity gives no accurate picture of acid secreting ability of the stomach because of neutralization of chloride by alkaline duodenal contents In the present experiments which lasted approximately one hour, there was no evidence of duodenal regurgitation insofar as presence of bile is an indication, and furthermore, we were working with pure gastric juice uncontaminated by test-meal or saliva Under these conditions we found, as did Berglund et al (8), that the curves of titratable acidity and total chloride were practically parallel Chart 5 shows the results in three patients The upper line in each case gives the total chloride, the lower the titratable acidity calculated as chloride Chart 6 serves a similar purpose Each dot of the lower set indicates the highest titratable chloride in a different case Two instances of anacidity are included for comparison The upper line gives the total chloride (concentration) in the corresponding cases The total chloride exceeds the titratable by a fairly uniform amount regardless of whether the titratable acidity is high or low In the first four cases, with little or no titratable acidity, the difference varies from 236 to 345 mgm, in the remainder the difference varied between 97 and 196 mgm In other words, under the conditions of these experiments the titratable acidity is a fairly accurate measure of the chloride secreting capacity of the stomach and gives a genuine indication as to whether the latter is high or low We emphasize this point because of the stress which has recently been placed on the necessity of actually determining chlorides The difference between total chloride and titratable chloride, of course, represents chloride in combination That base as determined largely accounts for this difference will be shown later

Total chloride The concentration of chloride in the stomach juice gives only an incomplete picture of chloride secretion Chart 7 shows the total output per ten-minute period The great differences in different subjects are to be noted as well as the general similarity of form of the total chloride and volume curves (see chart 3) Chart 8

¹ Throughout this paper titratable acidity refers to the number of cc of N/10 NaOH necessary to neutralize 100 cc of gastric juice with di-methyl as indicator

expresses some other relations of chloride secretion Each dot in the lower line indicates the highest total output of chlorides per ten-minute period in a different case The upper line gives the concentra-

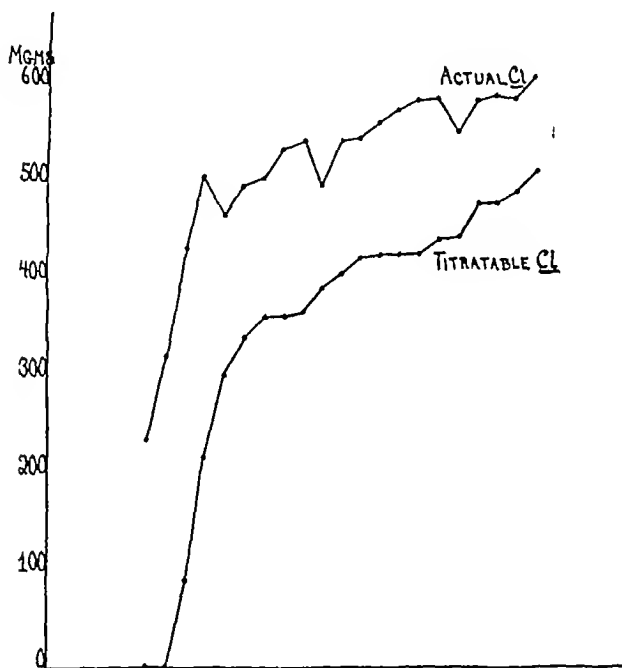


CHART 6 CHLORIDE (MGMS PER 100 CC) CALCULATED FROM HIGHEST TITRATABLE ACIDITY IN EACH CASE (LOWER LINE) AND CHLORIDE AS ACTUALLY DETERMINED BY ANALYSIS IN SAME SPECIMENS (UPPER LINE)

tion of chloride in the same specimens When the total output is extremely low the concentration is also low but in the majority of cases there is no correlation between the two values This chart

expresses in another way the essential facts brought out in chart 4. In brief, at a given concentration much or little chloride may be secreted

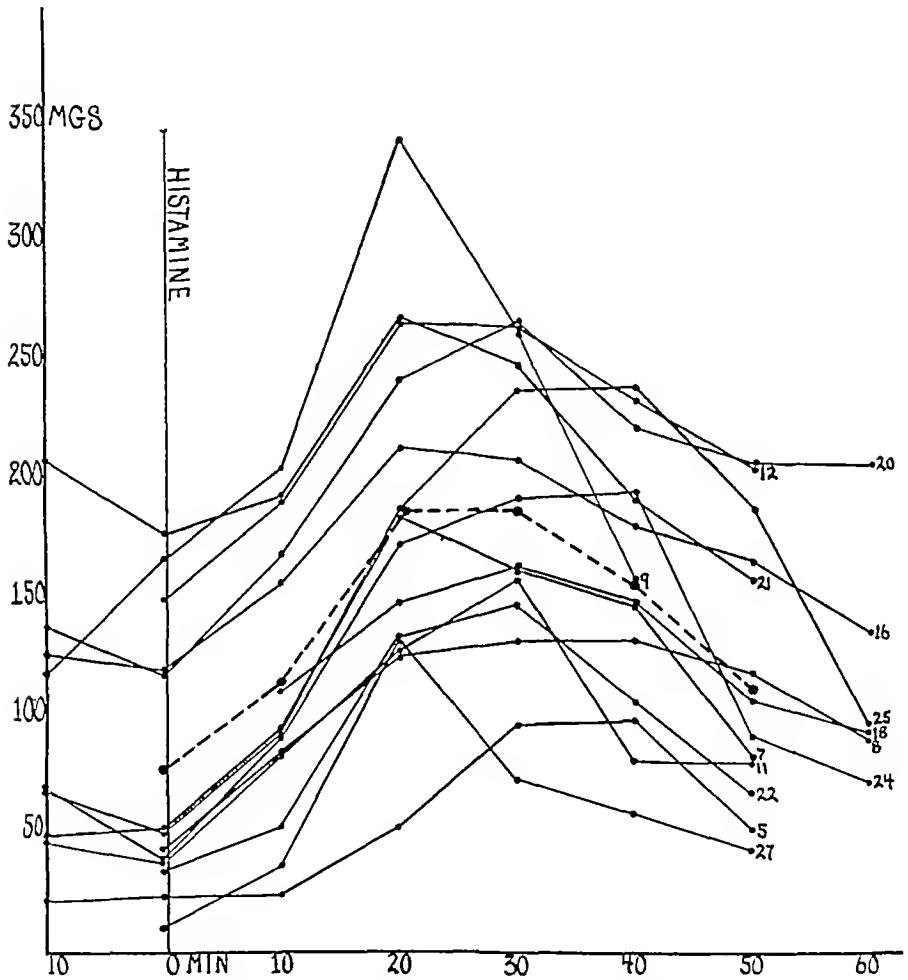


CHART 7 CURVES SHOWING QUANTITY (MG.) OF CHLORIDE SECRETED IN TEN-MINUTE PERIODS BEFORE AND AFTER HISTAMINE

Base

The question of concentration of base may next be considered, and the figures for the various ten-minute specimens are presented in

chart 9 The values in different cases are of the same general order of magnitude The most striking point is that while base is relatively high before stimulation, it thereupon falls promptly and reaches a low

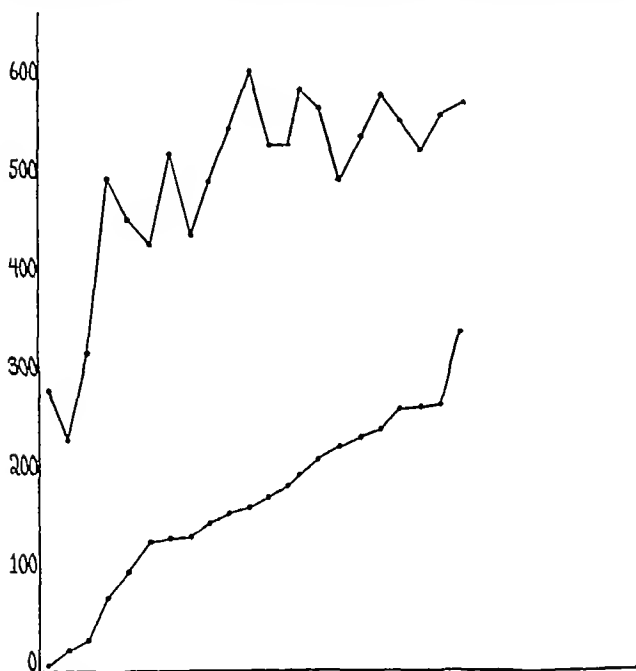


CHART 8 TOTAL OUTPUT OF CHLORIDE (MGM) PER TEN MINUTE PERIOD IN EACH CASE (LOWER LINE), CONCENTRATION OF CHLORIDE (MGM PER 100 CC) IN SAME SPECIMENS (UPPER LINE)

point after about thirty minutes This is well shown in the composite curve (broken line) In some cases (numbers 27, 22, 25) there was a rise toward the end of the experiment

It seemed possible that the fall in base was due simply to dilution by

line, chart 11) falls with fall in volume of juice without any corresponding rise in concentration within the limits of time of the present experiments. The concentration may rise later when the effects of stimulation have entirely passed and the volume of secretion is reduced to a minimum.

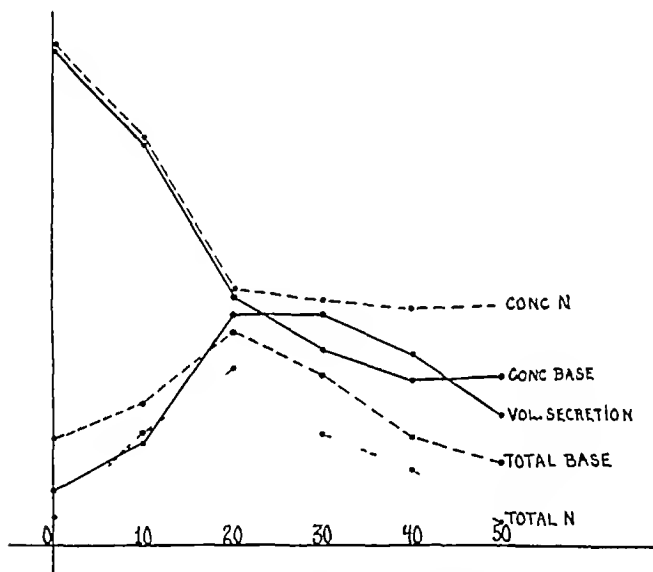


CHART 10 COMPOSITE GRAPH OF VOLUME OF SECRETION (CC), TOTAL BASE (mEq) CONCENTRATION OF BASE (mEq PER LITER) CONCENTRATION OF NITROGEN AND TOTAL NITROGEN IN TEN MINUTE PERIODS BEFORE AND AFTER HISTAMINE

Calculations were next made to find out to what extent the discrepancy between titratable and total chloride could be accounted for by base. The solid lines in chart 12 represent a composite calculation for the six cases shown in chart 9. The figures for the calculated acidity were reached by subtracting from the milliequivalents of chloride the milliequivalents of base for the corresponding periods.

increased secretion That this explanation is untenable is indicated by chart 10, in which the concentration of base (composite) in the six cases of chart 9, is shown together with a composite volume curve from the same cases At first glance these curves seem to be the reverse of each other but further inspection shows that during the overlapping portion of their course *both are falling* In brief, the concentration of base fell not only when volume of secretion was increasing but also

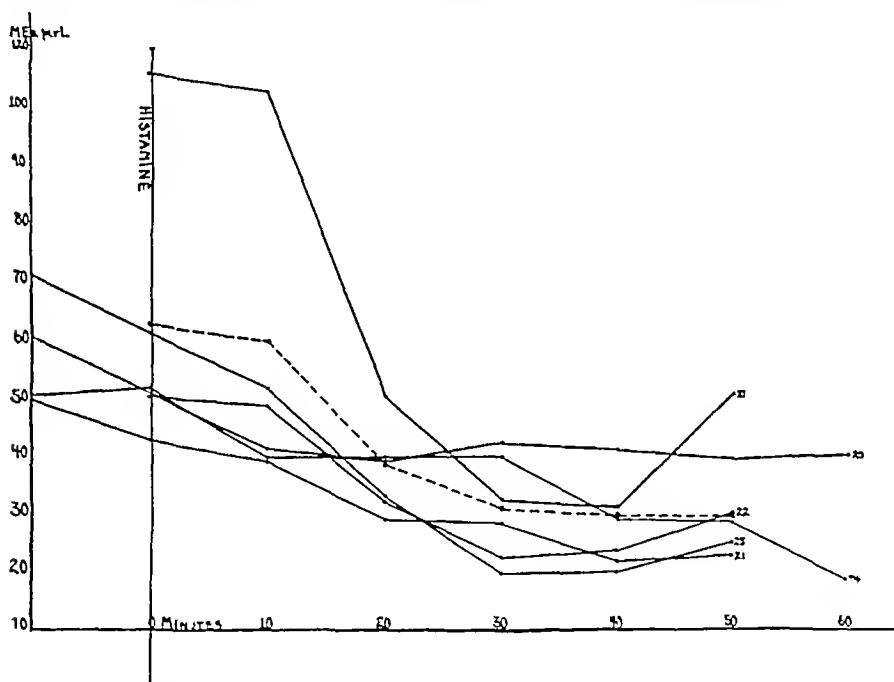


CHART 9 CONCENTRATION OF BASE (mEq PER LITER) OF GASTRIC JUICE AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

when it was decreasing This rules out a mere dilution effect as do the observations depicted in chart 11, which shows the total *quantity* of base put out per ten-minute period Here one sees that while the concentration *falls* the output *increases* after stimulation and that the total amounts vary considerably in different cases They parallel quite closely the volume of secretion as may be seen by further reference to chart 10 It is clear, therefore, that the secretion of base is actively affected by histamine stimulation The total output (broken

line, chart 11) falls with fall in volume of juice without any corresponding rise in concentration within the limits of time of the present experiments. The concentration may rise later when the effects of stimulation have entirely passed and the volume of secretion is reduced to a minimum.

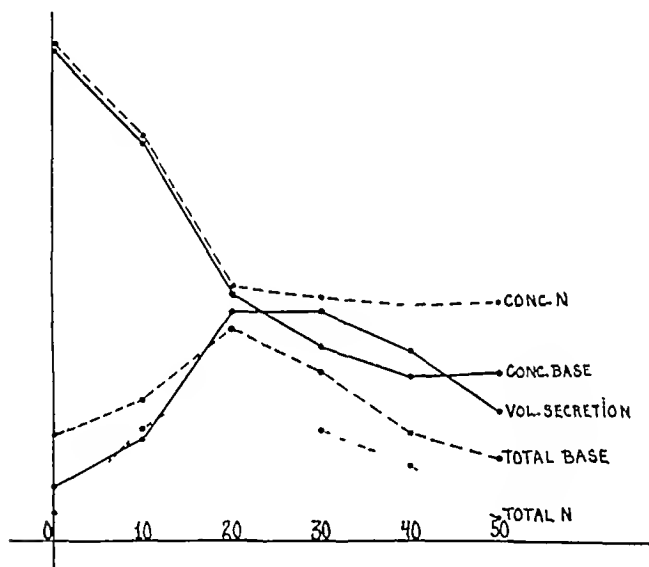


CHART 10 COMPOSITE GRAPH OF VOLUME OF SECRETION (CC.), TOTAL BASE (mEq) CONCENTRATION OF BASE (mEq PER LITER) CONCENTRATION OF NITROGEN AND TOTAL NITROGEN IN TEN MINUTE PERIODS BEFORE AND AFTER HISTAMINE

Calculations were next made to find out to what extent the discrepancy between titratable and total chloride could be accounted for by base. The solid lines in chart 12 represent a composite calculation for the six cases shown in chart 9. The figures for the calculated acidity were reached by subtracting from the milliequivalents of chloride the milliequivalents of base for the corresponding periods.

The "actual" acidity is that determined by titration with $N/10$ NaOH against dimethyl. When secretion is under way the calculated figures are uniformly higher than the "actual" and it is evident that the difference between titratable acid and total chloride is not completely accounted for by base, although the discrepancy is not large. The broken lines in chart 12 show the findings in a single representative

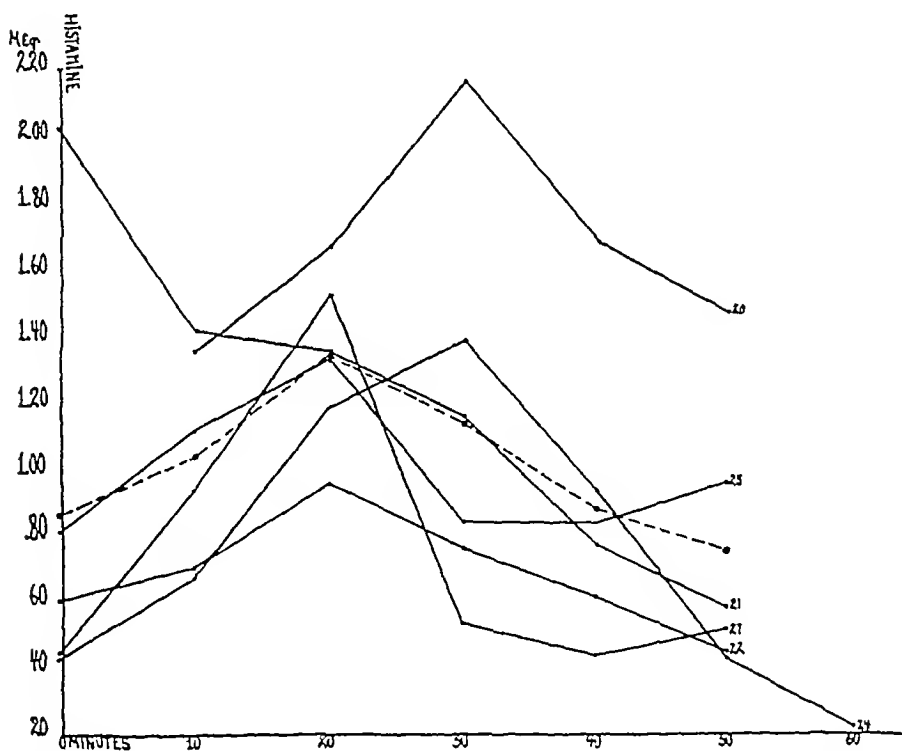


CHART 11 CURVES OF TOTAL BASE (mEq) SECRETED IN EACH CASE IN TEN-MINUTE PERIODS

case. The fact that actual is above calculated acid in the first part of the curve in chart 12 is due to the absence in some cases of titratable acid with dimethyl before stimulation, as there is no figure to express value less than zero an artefact is introduced. The slight discrepancy between the calculated and actual acidity must be due to some buffer substance, possibly protein. This point will be discussed below.

Charts 13 A and B show the course of events as regards *concentration*. The separation of the curves after stimulation, owing to rise in chloride and drop in base, is obvious. The crossing of the lines in case twenty-seven indicates that the specimens were actually alkaline before secretion became marked. The numbers on the acid line refer to the titrat-

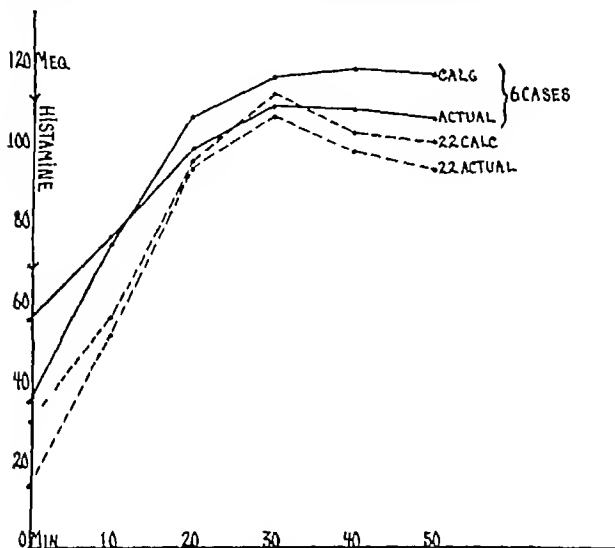


CHART 12 GRAPHS SHOWING GASTRIC ACIDITY AS DETERMINED BY DIRECT TITRATION OF JUICE (FREE HCl) AND ACIDITY OF SAME SPECIMENS CALCULATED BY SUBTRACTING BASE FROM CHLORIDE CONCENTRATION DETERMINED UPON SAME SPECIMENS

Shows curves from a single case (no 22) and composite curves of six cases

able acidity at various points. Their failure to correspond exactly with the difference between acid and base is discussed in the paragraph above. Charts 14 A and B show the *total quantities* of acid and base secreted in ten-minute periods. In contrast to the preceding curves the total quantity of base increases even though the concentration

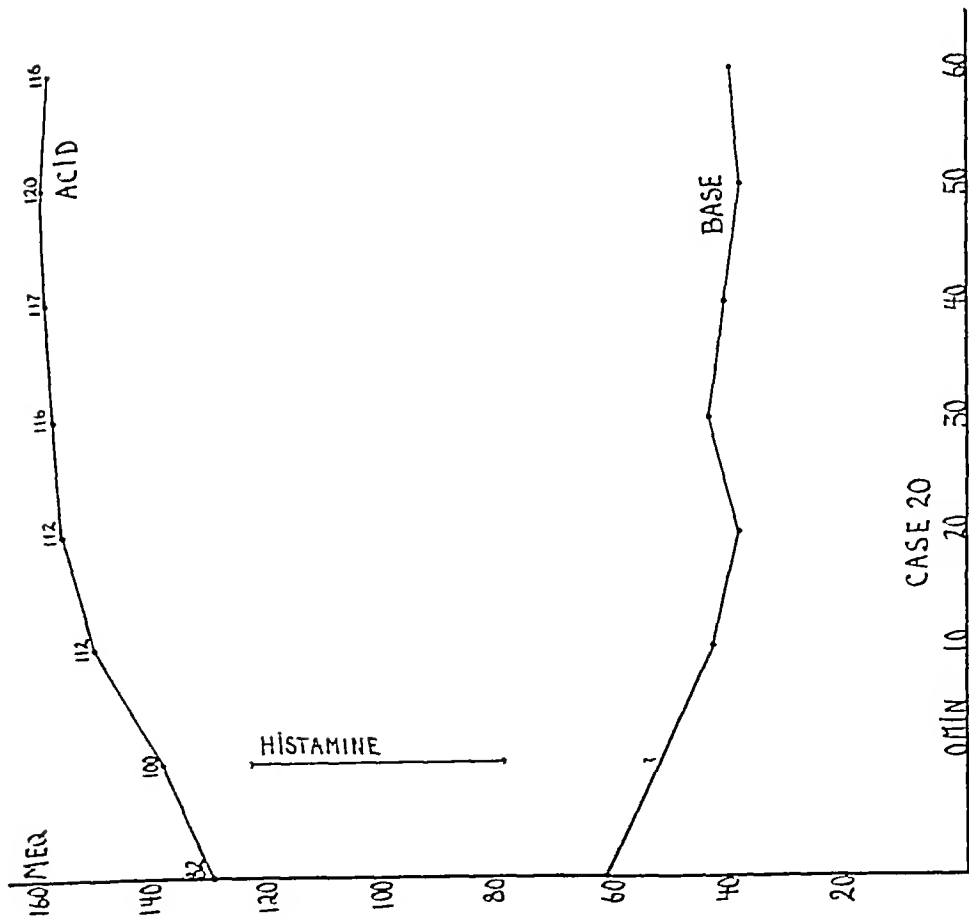


CHART 13, A

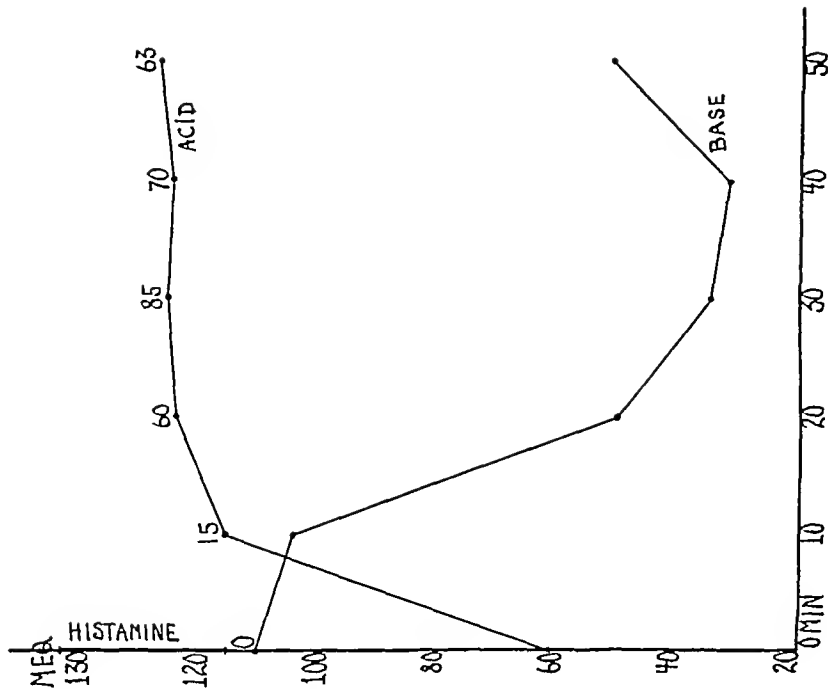


CHART 13, B

CHARTS 13, A AND B SIMULTANEOUS CURVES OF CONCENTRATION OF CHLORIDE AND OF BASE AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE IN RELATION TO TITRATABLE ACIDITY (FREE HCl)

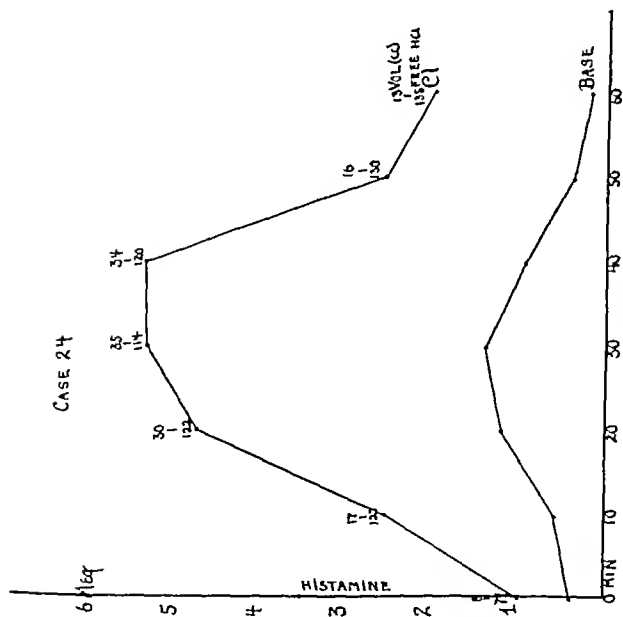


CHART 14, A

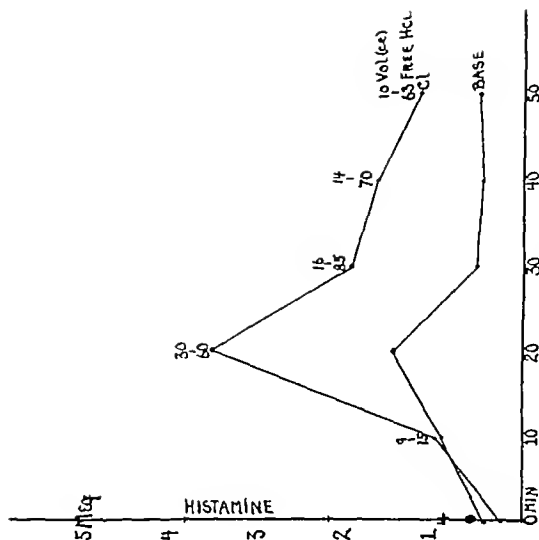


CHART 14, B

CHARTS 14, A AND B TOTAL OUTPUT OF CHLORIDE AND BASE (mEq) IN TEN MINUTE PERIODS, IN RELATION TO TITRATABLE ACIDITY AND VOLUME OF SECRETION

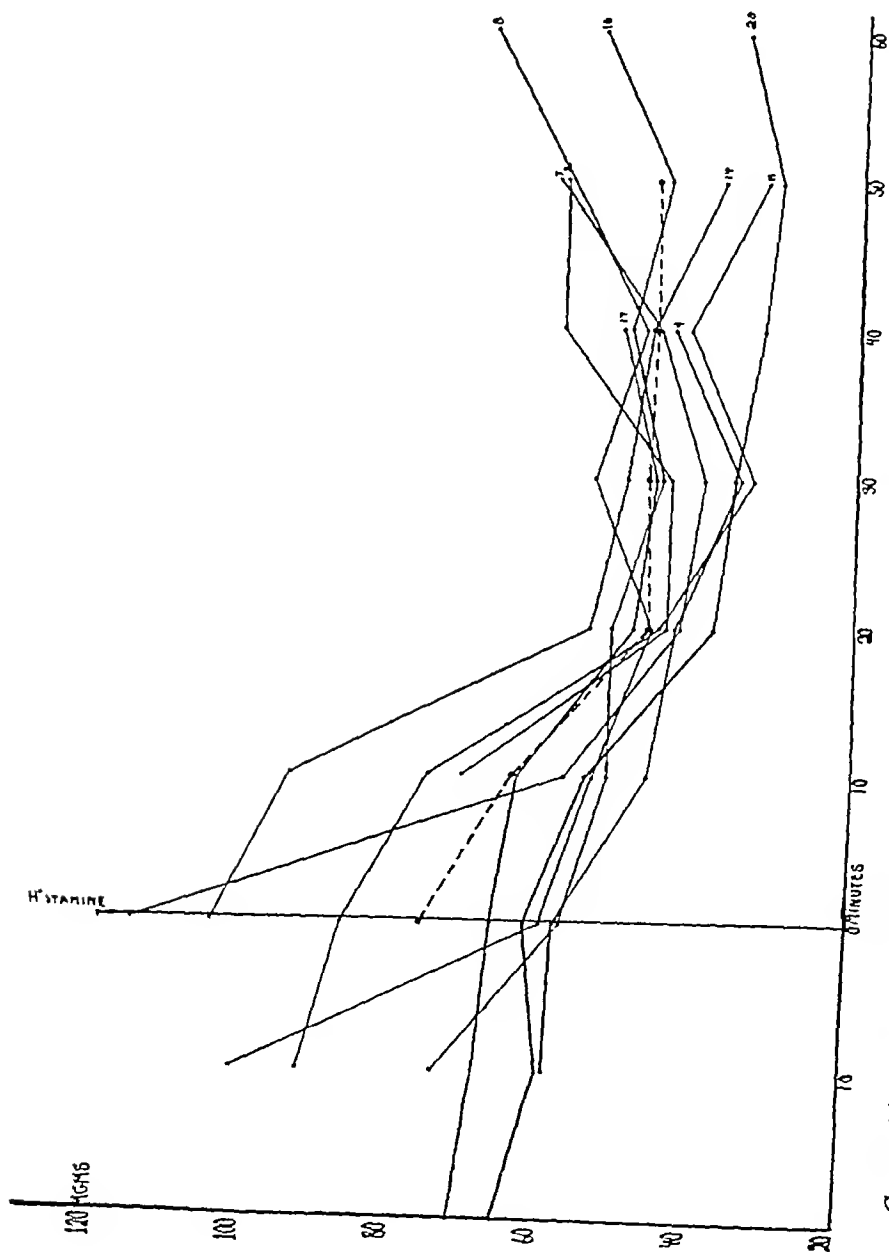


CHART 15 NITROGEN CONCENTRATION (MCM PER 100 CC) AT TEN-MINUTE INTERVALS BEFORE AND AFTER HISTAMINE

falls. The volume of secretion and titratable free HCl are also indicated above the chloride line. The importance of taking volume of secretion into account is clearly brought out. In case 24, for example, during the forty to fifty-minute period the excess of chloride over base is much less than during the preceding period. In spite of this the titratable acidity is slightly higher. This is clearly explained by the fall in volume of secretion from 34 to 16 cc.

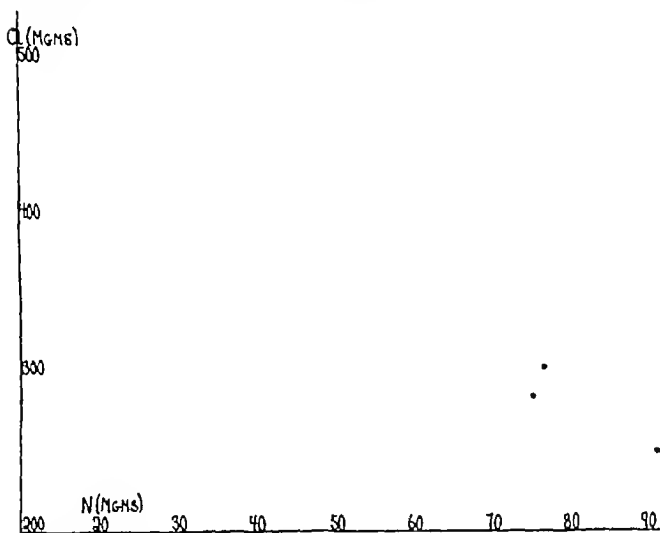


CHART 16 RELATION OF CONCENTRATION OF NITROGEN TO CONCENTRATION OF CHLORIDE IN VARIOUS SPECIMENS

Concentration of nitrogen Chart 15 shows the figures for concentration of nitrogen in eight cases, and the composite curve (broken line) indicates the general trend of events, there is a distinct fall after stimulation, followed by a sustained low level, and after an hour, a rise. The same reasoning as in the case of base was applied to show that these variations in nitrogen were not due simply to dilution. Chart 16 gives nitrogen values plotted against the chloride concentra-

tion of the same specimens. A definite inverse relation is evident. Furthermore, as in the case of base, the total amounts of nitrogen

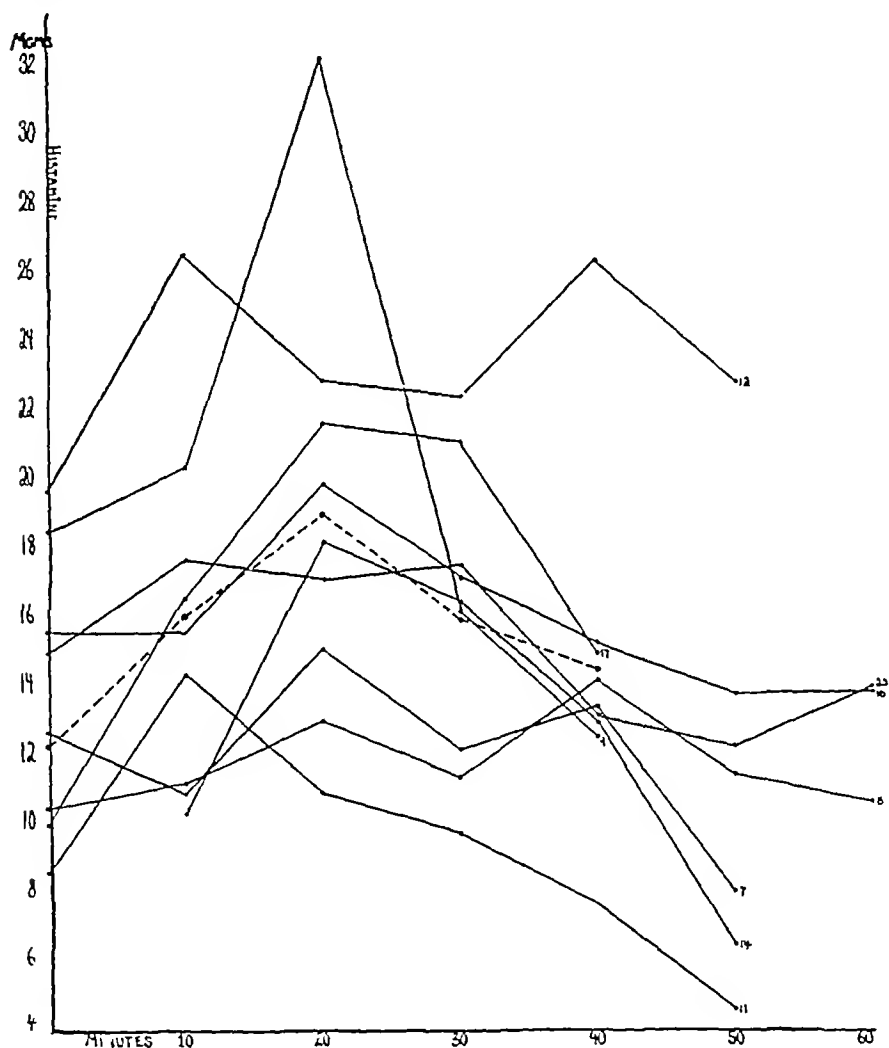


CHART 17 CURVES SHOWING TOTAL NITROGEN (MGM) OF GASTRIC JUICE FOR TEN-MINUTE PERIODS BEFORE AND AFTER HISTAMINE

secreted over ten-minute periods in general *increase* after stimulation (see chart 17). Briefly, all the curves of nitrogen and base are strik-

ingly similar (see chart 10) This fact seems of importance in so far as such a close relationship suggests a possible association between the secretory mechanisms for the two The actual values of nitrogen concentration may be compared with those of the blood and are found to be much smaller Urea nitrogen was estimated in one case (number 16) and represented approximately one-tenth of the total nitrogen

DISCUSSION

On the basis of the above facts one may now discuss the sequence of events in gastric secretion The fasting stomach, in the case of our subjects, under basal conditions, secreted a relatively small amount of juice with low chloride and high base and nitrogen content. After histamine stimulation there was an increase in the volume of secretion with increase in concentration of chloride and of total chloride output, and with decrease in concentration of nitrogen and base but with increase of the total quantity of these substances The first evidence of cessation of secretion was a fall in the volume of juice with drop in total output of all its elements, later the concentration of nitrogen and base rose and the concentration of chlorides in the mixed juice fell The importance of determining the total output of the various constituents should be specially emphasized Unless total quantities are determined one can obtain no accurate idea of the rate of secretion which is the truest index of gastric function, the concentration of chloride, for example, may be the same in two people who, per unit of time secrete very different amounts of chloride

From the clinical standpoint one is interested in the validity of the titratable acidity as an index of acid secreting capacity of the stomach Our observations indicate that provided pure gastric juice (i.e., juice undiluted by test meal) is examined the titratable acidity at the height of secretion does furnish such an index inasmuch as it falls short of the actual chloride secretion by a relatively constant amount Chloride concentration indicates the highest potential acidity of the gastric secretion, the actual free acidity depends upon the amount of base and other neutralizing substance present Duodenal regurgitation apparently played no part in the present experiments

We have studied our protocols to see if any light could be thrown on the fundamental mechanism of gastric secretion No methods have as

yet been devised which make it possible to analyze the secretion of individual gastric cells or groups of cells, the contents of the tubules represent a composite secretion which may undergo various alterations before actual discharge into the stomach. An analysis of mixed gastric juice is therefore at best far removed from the events which take place at secreting cell surfaces. Most students of gastric physiology believe that at least two types of cell—the peptic and the acid—have different secretory functions. The similarity between our curves for base and nitrogen suggest that these substances are perhaps put out by the same cells, whereas the acid may arise from others. The relation of the curve of peptic activity to the nitrogen curve is now being studied. It may be, as many have suggested (18), that the acid cells secrete an unstable chloride which is hydrolyzed with the liberation of HCl , the base being retained or resorbed. This process is obviously enhanced during active secretion. Base and nitrogen may be secreted by different groups of cells. Be this as it may, in actual fact there is, in our observations, a general relationship between the various elements of gastric secretion which suggests that all of the cells give a coordinated response to histamine stimulation.

SUMMARY

Curves are presented which show the course of gastric secretion before and after histamine stimulation. The volume of secretion, the concentration of chloride, base and nitrogen and the total chloride, base and nitrogen have been studied. Increase in titratable acidity after stimulation results from greater increase in output of chloride than of base. Nitrogen secretion seems to parallel secretion of base and hence may be related to it, at any rate, nitrogen is actively secreted by the stomach.

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